



AMERICAN KENNEL CLUB
**CANINE HEALTH
FOUNDATION**
PREVENT TREAT & CURE®
SINCE 1995

2018 Research Grants Portfolio



Introduction

June 1, 2018

For the past 23 years the AKC Canine Health Foundation (CHF) has remained committed to addressing the health needs of our closest companions through the funding of scientific research, and by providing educational resources for those dedicated to improving the health of dogs.

This grants portfolio represents active research projects, funded through CHF, categorized by research program area, and selected to advance the Foundation's Mission for the betterment of health for all dogs. Every grant proposal goes through a rigorous assessment by the CHF Scientific Review Committee (akcCHF.org/Scientific-Review-Committee) and by peer reviewers representing a diverse set of experts from across the scientific community. Each grant is assessed for scientific merit, impact in the field of study, and significance to dogs and their people through One Health. The peer-review process ensures the contributions of our donors will be directed to studies that have the greatest potential benefit for dogs. The study abstracts listed on the following pages represent cutting edge research as well as applied clinical studies chosen to improve the lives of dogs as well as contribute to our understanding of complex disease processes, including genetics. The program areas funded by CHF represent a broad range of concerns across general canine health as well as within specific breeds. Through defined research program areas, CHF considers areas of unmet health needs and areas of immediate opportunity, while applying recent advancements in science and technology to canine health research.

The recent research initiatives directed by CHF to address tick-borne diseases and epilepsy are reflected in this portfolio, and include publication outcomes and educational resources at these weblinks, akcCHF.org/ticks and akcCHF.org/epilepsy. CHF is also bringing novel approaches to hemangiosarcoma this year through a research initiative which includes several newly funded projects that use innovative and cross-institutional tactics to find solutions for this devastating disease. Additional work currently funded in other areas of oncology, heartworm disease, neurology, Addison's disease and across all CHF research program areas is contained within this portfolio and can also be searched online at akcCHF.org/research/our-research/.

In addition to CHF's wide array of research grants, the Foundation remains dedicated to educating the next generation of scientists by providing funds through the AKC Canine Health Foundation Clinician-Scientist Fellowship Program (akcCHF.org/about-us/who_we_are/Fellows/). Also, through the collaborative efforts of the American Kennel Club, AKC Canine Health Foundation and the Theriogenology Foundation, the AKC/AKCCHF/TF Theriogenology Residency Program increases the number of trained practitioners in the field of companion animal theriogenology. Through outreach to breeders, veterinarians and the general public, we also provide resources and communications on outcomes of research and important topics for canine health. (akcCHF.org/research/)

As you look through the following pages please do so knowing these studies will lead to a better understanding of canine health concerns that will advance the prevention, treatment and cures of canine diseases. To discuss a study or to learn about sponsoring research, please contact us at chfgrants@akcCHF.org. We want to hear from you. Together, we are moving canine health research forward, benefiting the dogs who so enrich peoples' lives.

Because of the support of our partners at the American Kennel Club, Purina, Elanco, OFA, Zoetis, and the many breed clubs, foundations and private donors whose support we so value, 2018 continues to be another productive year for the AKC Canine Health Foundation.

Thank you from the CHF staff and Board of Directors, and from the dogs whose lives are positively impacted by this work through your efforts and generosity.

Sincerely,

Diane Brown

Diane Brown, DVM, PhD, DACVP
Chief Executive Officer/Chief Scientific Officer

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02518

New

The Effects of Early Life Experience on Working Dog Temperament and Cognition**Principal Investigator:** Emily E. Bray, PhD; University of Arizona**Total Grant Amount:** \$105,949**Grant Period:** 5/1/2018- 4/30/2020

Project Abstract: Working dogs provide irreplaceable services and support to their handlers and communities. However, only around 35% of dogs bred for this purpose are ultimately successful. Therefore, improvements to methods for working dog breeding, rearing, training and selection could lead to major advances including increases in the supply of trained dogs and reductions in the expense required to train them. Some of the earliest, yet most formative, interactions that occur in a mammal's life are those involving its mother, and yet, best canine mothering practices are not well-established or studied. In collaboration with Canine Companions for Independence, the investigators will quantitatively assess levels of maternal behavior in order to: 1) examine associations between maternal behavior and offspring temperament, cognition and neuroendocrine profiles at eight weeks of age; 2) compare maternal style and puppy behavioral, cognitive, and neuroendocrine profiles between different types of early rearing environments (private home versus professional center); and 3) identify temperament and neuroendocrine predictors of individual differences in maternal style. These components will reveal how differences in the early environment affect working dog development, and the extent to which individual differences in maternal style can be predicted from temperamental and neuroendocrine characteristics of the dam. This research will provide foundational data regarding how early-life experiences influence puppy development, and how these processes can be optimized to promote the healthy development of dogs well-suited to the demands of diverse working roles.

Blood Disorders

02515-A

Investigating the Role of Interleukin-17-producing Cells in the Pathophysiology of Canine Immune Mediated Hemolytic Anemia**Principal Investigator:** Shauna L. Blois, DVM; University of Guelph**Total Grant Amount:** \$8,690**Grant Period:** 4/1/2018– 7/31/2019

Project Abstract: Canine primary immune-mediated hemolytic anemia (IMHA) is an acute and severe disease of dogs with a mortality rate ranging up to 70%. IMHA is caused when the immune system produces abnormal antibodies that attack and destroy the dog's own red blood cells. It is not known how or why these abnormal antibodies form in the body. Increased levels of certain inflammatory cytokines (small proteins that affect cells) could cause the production of abnormal antibodies leading to IMHA, and many cells in the body, most notably the white blood cells, produce these cytokines. Autoimmune hemolytic anemia (AIHA) is a disease of humans that shares similarities to canine IMHA. As the causes of human AIHA are better understood, novel treatments are being discovered. Increases of a particular cytokine, interleukin (IL)-17, were recently found in people with AIHA. Additionally, targeted therapy to reduce IL-17 levels improved disease condition in AIHA models. The investigators recently identified increased IL-17 in blood of dogs with IMHA and will study its role in the cause of this disease. This study will specifically identify and measure the types of white blood cell(s) in the body that produce IL-17 which could lead to further understanding of the cause(s) of IMHA in dogs and help uncover new treatment targets for this disease.

02536-MOU

Immunoprofiling to Combat Canine Immune Thrombocytopenia**Principal Investigator:** Marjory B. Brooks, DVM; Cornell University and Dana LeVine, DVM, PhD; Iowa State University**Total Grant Amount:** \$16,106**Grant Period:** 8/1/2018- 1/31/2020**Project Abstract:**

Autoimmune disease develops in dogs when their immune system destroys normal healthy cells in the body. Immune thrombocytopenia (ITP) is a serious bleeding disorder that results from immune destruction of platelets, small blood cells that play a critical role in preventing bruising and bleeding after injury. Old English Sheepdogs and Cocker Spaniels appear to have a susceptibility to ITP, however, ITP afflicts all dogs regardless of breed. Dogs with ITP develop bruises and, in the most severe cases, may bleed from the intestinal and urinary tract or have fatal blood loss. Fortunately, most dogs survive ITP, but may relapse months to years after a first episode. The treatment of ITP involves protracted courses of potent immunosuppressive drugs that impact quality of life for both dog and owner. This study will use a genetic approach to understand what causes ITP. The investigators will identify laboratory markers that predict bleeding severity to aid veterinarians in treatment selection. The goals of this research are to improve ITP diagnosis and predictions of relapse, leading to targeted therapies that minimize treatment side effects. *Funding for the research is provided through the collaborative efforts and generosity of Old English Sheepdog Club of America and English Cocker Spaniel Club of America Health and Rescue Organization. The AKC Canine Health Foundation supports the funding of this effort and will oversee administration of funds and scientific progress reports.*

02355-A

Hyperlipidemia in the Miniature Schnauzer: A Combined Metabolomic and Genomic Approach

Principal Investigator: Christopher A. O'Callaghan, MD, PhD; University of Oxford

Total Grant Amount: \$14,958

Grant Period: 8/1/2017–1/31/2019

Project Abstract: Miniature Schnauzers can be affected by a condition causing too much circulating lipid (fat) in the bloodstream, known as hyperlipidemia. The problem appears to worsen as dogs get older and may affect up to 3 in every 10 dogs. Affected dogs are more likely to suffer from other serious health conditions including pancreatitis and diabetes, and liver and kidney problems. Whilst an underlying genetic cause is suspected, the gene(s) responsible for this condition in Miniature Schnauzers have not been identified. At present, routine blood tests only allow veterinarians to measure 2 types of lipid: triglyceride and cholesterol. In contrast, improved diagnosis and personalized treatment options have been achieved in human lipid disorders by measurement of a much wider variety of lipids in the bloodstream, combined with genetic testing. The investigators will measure over 2000 substances including lipid- and metabolism-related markers in the blood of Miniature Schnauzers to improve understanding of hyperlipidemia that may guide more specific treatment options. The researchers will also examine differences between genes of affected and unaffected Miniature Schnauzers to try to identify important mutations associated with hyperlipidemia. These studies may lead to a genetic screening test and/or new targets for treatment of this condition.

02348

Whole Blood Transcriptome Profiling of Dogs with Immune-Mediated Hemolytic Anemia (IMHA)

Principal Investigator: Steven G. Friedenberg, DVM, PhD; University of Minnesota

Total Grant Amount: \$53,471

Grant Period: 4/1/2018- 3/31/2020

Project Abstract: Immune-mediated hemolytic anemia, or IMHA, is a common autoimmune disease in dogs in which the body's immune system attacks its own red blood cells. Red blood cells are critical for transporting oxygen. Many dogs affected by IMHA require extensive hospitalization and blood transfusions, and often have fatal disease-related complications. While dogs of every breed can get IMHA, many Spaniel breeds are overrepresented. Despite its high morbidity and mortality, IMHA and its triggers are still not well understood, which hinders the potential to develop treatments and stop this disease in its early stages. In this study, the investigators will use RNA sequencing to evaluate the genes that are active in the blood of dogs who have been newly diagnosed with IMHA. Comparing this data with that of healthy dogs without IMHA will allow the investigators to determine which genes are turned on in the early stages of IMHA. Additionally, this data may have future use in determining if any specific genetic changes are associated with activating these early onset genes. The investigators hope to identify genes which might be novel therapeutic targets for intervention in IMHA, and identifying specific variants in these genes may improve understanding of which dogs are at risk for developing IMHA.



Cardiology

02531

Identification of Genetic Risk Allele(s) Associated with the Development of Tricuspid Valve Dysplasia in the Labrador Retriever

Principal Investigator: Kathryn M. Meurs, DVM, PhD; North Carolina State University

Total Grant Amount: \$57,158

Grant Period: 6/1/2018- 5/31/2020

Project Abstract: Tricuspid valve dysplasia is an inherited heart defect that is characterized by an abnormally formed tricuspid valve on the right side of the heart. It is reported to be most commonly observed in the Labrador Retriever although it has been observed in a few other breeds including the Boxer and Golden Retriever, among others. Although some affected dogs only have a very mild valve malformation and can live quite comfortably with the defect, others are born with a very abnormal valve that results in heart valve leakage and the eventual development of congestive heart failure. Tricuspid valve dysplasia has been shown to be an inheritable trait in the Labrador Retriever. The investigators will study and compare the genome sequences for affected and unaffected dogs. If successful, this study will identify a genetic marker for tricuspid valve dysplasia in the Labrador Retriever and which can be used to develop a strategy to gradually reduce the prevalence of the genetic variant and tricuspid valve dysplasia in the Labrador Retriever.

This research is generously supported by the Labrador Retriever Club of the Potomac Top Twenty Gala Foundation and the Labrador Retriever Club, Inc.



New

02521-MOU

Identification of Genetic Markers for Familial Subvalvular Aortic Stenosis in Golden Retrievers

Principal Investigator: Joshua A. Stern, DVM, PhD; University of California, Davis

Total Grant Amount: \$51,880

Grant Period: 2/1/2018- 1/31/2020

Project Abstract: Subvalvular Aortic Stenosis (SAS) is a heart defect characterized by a fibrous ridge located below the aortic valve. Affected dogs are at risk of developing heart valve infections, congestive heart failure or sudden death. Severely affected dogs have an average lifespan of 19 months. SAS is an inherited heart problem reported in Golden Retrievers. Studying this disease in Golden Retrievers has the potential to identify causative genetic mutations and develop a reliable genetic test for this condition. Ultimately, the identification of a mutation would aid breeders in making informed decisions to reduce the prevalence of this condition. The investigators will study the pattern of inheritance and conduct a genome wide association study (GWAS). Once a chromosomal region of interest is identified, whole genome sequencing (WGS) will be employed to identify variants associated with SAS. The top variants will then be studied using Sequenom analysis to prioritize variant pursuit.

Funding for the research is provided through the collaborative efforts and generosity of the Golden Retriever Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.

02520-MOU

Identification of Genetic Markers for Familial Subvalvular Aortic Stenosis in Rottweilers

Principal Investigator: Joshua A. Stern, DVM, PhD; University of California, Davis

Total Grant Amount: \$44,320

Grant Period: 2/1/2018- 1/31/2020

Project Abstract: Subvalvular Aortic Stenosis (SAS) is a heart defect characterized by a fibrous ridge located below the aortic valve. Affected dogs are at risk of developing heart valve infections, congestive heart failure or sudden death. Severely affected dogs have an average lifespan of 19 months. SAS is an inherited heart problem reported in Rottweilers. The goal of this research is to identify causative genetic mutations and develop a reliable genetic test for this condition in Rottweilers, to aid breeders in making informed decisions to reduce the prevalence of this condition. Once a chromosomal region of interest is identified via a genome wide association study (GWAS), whole genome sequencing (WGS) will be employed to identify variants associated with SAS. The top variants identified via WGS will be submitted for Sequenom analysis to prioritize variant pursuit.

Funding for the research is provided through the collaborative efforts and generosity of the Rottweiler Health Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.

02436

New

Predicting Disease Stage and Diuretic Responsiveness in Dogs with Acquired Heart Disease

Principal Investigator: Mark Papich, DVM; North Carolina State University

Total Grant Amount: \$41,731

Grant Period: 5/1/2018- 10/31/2019

Project Abstract: Congestive heart failure (CHF) causes difficulty breathing because of fluid accumulation in the lungs. It is an important and common clinical problem. Mitral valve regurgitation and dilated cardiomyopathy are common causes of CHF in dogs, which can develop as these conditions progress in severity. Because there currently is no cure for these heart diseases, the treatment focus has been on prolongation of the time to CHF development, relieving signs of fluid retention when CHF occurs, and supporting the function of a failing heart. Diuretic medications ("water pills") cause increased urination after removal of fluid from the lungs and are the most effective treatment for CHF. Most dogs respond to diuretics initially, but over time, progression of heart disease and maladaptive mechanisms result in less urine production and return of CHF signs with potential for suffering, death, or euthanasia. Loss of responsiveness to diuretic medications may be multifactorial, and so identification of the underlying reason could guide medical interventions to restore urine production in response to diuretics, and improve quality of life for dogs. The investigators have identified several candidate blood and urine variables that correlate with urine production in dogs and may be useful to indicate responsiveness to diuretic medications. This study will evaluate these variables in dogs with progressive stages of naturally occurring heart disease to identify those that are poorly responsive to diuretic medications and determine underlying causes for improved patient outcomes.

02424

Identification of Genetic Variants Associated with Pulmonary Valve Stenosis in Bulldogs through Whole-Genome Sequencing

Principal Investigator: Joshua A. Stern, DVM, PhD; University of California, Davis

Total Grant Amount: \$56,880

Grant Period: 4/1/2018- 3/31/2019

Project Abstract: Pulmonary valve stenosis (PS) is a devastating inherited heart disease in dogs and children. It is the most common congenital heart disease in dogs, with Bulldogs being overrepresented. PS is caused by abnormal anatomy of the pulmonary valve that limits ejection of blood into the lungs. Untreated dogs are at risk of sudden death, congestive heart failure, and may die before five years of age. The type of PS (A or B) and presence of abnormal coronary arteries heavily influence prognosis. While treatment aims to open the narrowed valve region, it is expensive, palliative, and not always effective at resolving the clinical condition. Studying the disease in Bulldogs has the potential to identify a genetic mutation for genetic testing. A prior study performed by the investigators has identified chromosomal regions likely to contain mutations for PS Types A/B and coronary anomalies in the breed. Whole genome sequencing will be used to investigate the regions to identify variants of interest that segregate with the disease. If identified, the results can be used to aid breeding practices to reduce the prevalence of this disease. Additionally, identification of the molecular basis of PS and coronary anomalies may help elucidate novel therapeutic or diagnostic strategies for this condition.

02389-MOU

Characterization of Ventricular Arrhythmias in Rhodesian Ridgebacks

Principal Investigator: Kathryn M. Meurs, DVM, PhD; North Carolina State University

Total Grant Amount: \$26,919

Grant Period: 9/1/2017- 8/31/2020

Project Abstract: The investigators recently identified a genetic mutation associated with heart arrhythmias in Rhodesian Ridgebacks. Dogs with the mutation appear to be at the most risk of developing an arrhythmia and suffering sudden death between 12-24 months of age, however, this timeline is variable, and some dogs appear to outgrow the arrhythmia. Due to the lack of knowledge of the specific at risk age, owners of dogs with the mutation must repeat the Holter monitor (a test to monitor heart rhythm) every few months to identify when their dog is at greatest risk and may need treatment. The objective of this study is to repeatedly perform regular Holter monitor testing on dogs with the mutation (including dogs with one copy and with two copies) every 4 months from 6-24 months of age with a final evaluation at 36 months to narrow in on the age when the arrhythmias appear to be the most severe. Gaining this increased clinical understanding of the disorder will decrease the risk of sudden death by helping owners and veterinarians in monitoring and providing treatment intervention for their dogs, and will further inform breeders and owners by characterizing the clinical and genetic manifestations of the disorder. *Funding for the research is provided through the collaborative efforts and generosity of the Rhodesian Ridgeback Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

02388-MOU

Genetic Markers for Familial Subvalvular Aortic Stenosis in Newfoundlands

Principal Investigator: Joshua A. Stern, DVM, PhD; University of California, Davis

Total Grant Amount: \$58,949

Grant Period: 9/1/2017- 8/31/2019

Project Abstract: Subvalvular Aortic Stenosis (SAS) is a heart defect characterized by a fibrous ridge located below the aortic valve. Affected dogs are at risk of developing heart valve infections, congestive heart failure or sudden death. Severely affected dogs have an average lifespan of 19 months. A previous study identified a single gene mutation associated with a cohort of Newfoundland dogs with SAS, however this mutation does not explain all SAS in the breed and requires further evaluation. Studying this disease in Newfoundlands has the potential to identify causative genetic mutations and develop a reliable genetic test for this condition to further aid breeders to reduce the prevalence of this condition. The investigators will study pattern of inheritance and use the most modern genetic techniques to identify the genetic cause of SAS in Newfoundlands, further expanding our understanding of this disease in dogs. *Funding for the research is provided through the collaborative efforts and generosity of the Newfoundland Club of America Charitable Trust. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

02368

Identification of Mitral Valve Disease DNA Variants in Miniature Schnauzers

Principal Investigator: Kathryn M. Meurs, DVM, PhD; North Carolina State University

Total Grant Amount: \$56,635

Grant Period: 8/1/2017- 7/31/2019

Project Abstract: Mitral valve degeneration is the most common heart disease in the dog, and is particularly common in small breed dogs. Miniature Schnauzers are one of the most commonly affected breeds. Although some dogs live comfortably with the disease, many affected dogs die of congestive heart failure and sometimes sudden death due to rupture of a weakened heart. Mitral valve degeneration is thought to be an inherited disease in the dog although the causative mutation(s) have not been identified. Failure to understand the underlying cause of canine mitral valve degeneration has slowed the development of effective treatment and prevention plans. The investigators will identify genetic variants that lead to the development of mitral valve degeneration in Miniature Schnauzers, and use this information to develop treatment and prevention plans for dogs with high-risk DNA variants.

02327-MOU

Identification of Genetic Markers for Familial Subvalvular Aortic Stenosis in Bullmastiffs

Principal Investigator: Joshua A. Stern, DVM, PhD; University of California, Davis

Total Grant Amount: \$55,173

Grant Period: 4/1/2017- 3/31/2019

Project Abstract: Subvalvular Aortic Stenosis (SAS) is a heart defect characterized by a fibrous ridge located below the aortic valve. Affected dogs are at risk of developing heart valve infections, congestive heart failure or sudden death. Severely affected dogs have an average lifespan of 19 months. SAS is an inherited heart problem reported in Bullmastiffs and other breeds. Studying this disease in Bullmastiffs has the potential to identify a genetic mutation and develop a test for this condition. Ultimately the identification of a mutation in Bullmastiffs would aid breeders in making decisions to reduce the prevalence of this condition. The objective of this study is to use the most modern genetic techniques to identify the genetic cause of SAS in Bullmastiffs. The investigators have collected DNA samples from affected and unaffected Bullmastiffs and will study inheritance to identify genetic variants associated with SAS. *Funding for the research is provided through the collaborative efforts and generosity of the American Bullmastiff Association. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

01760-T

Use of Gene Therapy to Treat Dilated Cardiomyopathy

Principal Investigator: Margaret M. Sleeper, VMD; University of Florida

Total Grant Amount: \$146,774

Grant Period: 9/1/2016- 2/28/2019

Project Abstract: Dilated cardiomyopathy (DCM) is the second most common cause of heart disease in dogs, and medical management of the secondary signs is the only therapeutic option. The outcome for affected dogs depends on the stage of disease and the breed. Once diagnosed, dogs typically exhibit rapid and uniform progression to congestive heart failure (CHF), with most living less than 6 months. Previous research has shown that heart function is critically dependent upon calcium channel function. These gate-like channels found within the wall of cardiac muscle cells open and close, allowing calcium ions to flow into the cell. Calcium influx then regulates muscle contraction. Heart disease is strongly associated with malfunctioning calcium channels within cardiac cells. Gene transfer strategies to reduce calcium cycling abnormalities improve heart function in animal models as well as in human clinical trials. In this study, Dr. Sleeper will conduct a placebo-controlled, double blinded study to evaluate gene delivery approaches for treatment of Doberman Pinschers affected with DCM and CHF. If results show that the gene delivery slows progression of heart failure in Dobermans with DCM, the results will have significant ramifications for all dogs with heart disease, as calcium handling proteins are abnormally expressed in dogs with heart disease of varying causes.

Dermatology and Allergic Disease

02472-A

Effect of Lokivetmab on Tissue Biomarkers of Canine Atopic Dermatitis Using RNA Sequencing

Principal Investigator: Frane Banovic, DVM, PhD; University of Georgia

Total Grant Amount: \$9,747

Grant Period: 12/1/2017- 11/30/2018

Project Abstract: Atopic dermatitis (AD) is the most common, chronic, inflammatory and pruritic allergic skin disease that affects dogs worldwide. Treatment of canine AD has a high unmet need for effective and safe therapeutics. The transcriptome investigation of human AD tissues before and after treatment modalities has revolutionized the understanding of the molecular fingerprint of AD, further defining pathogenic immune pathways and identifying disease-specific biomarkers. In the early-phase trial, lokivetmab, a canine monoclonal antibody targeting interleukin-31 (IL-31) cytokine, markedly improved disease activity, but the effect of IL-31 blockade on AD at the genomic level has not been characterized. The investigators will evaluate lokivetmab modulation of the canine AD transcriptome (defined as differentially expressed genes between lesional and non-lesional skin) using next-generation RNA sequencing (RNA-seq). Findings may suggest that inhibition of a single target has the potential to reverse AD pathomechanisms, opening the door for new targeted treatment for this common and debilitating inflammatory skin disease. Furthermore, transcriptome analysis using RNA-seq may identify novel pathogenic pathways of inflammatory biomarkers as canine AD disease drivers, with potential for development of novel targeted therapeutics.

02241

The City Dog Study: Dermatologic and Respiratory Disease Among Inner-City Dogs Living in the Homes of Children with Asthma

Principal Investigator: Meghan F. Davis, DVM, MPH, PhD; Johns Hopkins University

Total Grant Amount: \$158,367

Grant Period: 2/1/2016- 1/31/2019

Project Abstract: Children who live in inner-city households of low economic means suffer disproportionately from skin and lung diseases, including asthma. This study will evaluate the burden of skin and respiratory disease among the dogs who live with them. These dogs often can be hard to study because their owners may not have the means or access to take them to the veterinarian. As an adjunct to a funded public health research effort targeting 200 children with asthma, Dr. Davis and her team will enroll 100 dogs and follow their health at three home visits over six months, and perform two additional evaluations. First, they will study the microbial (bacterial) communities on the dogs to determine how these change over time, and if the changes are associated with skin or respiratory diseases in the dogs. Then, the investigators will look at how the children and dogs share bacteria (i.e. microbiome). Early life exposures to dogs may protect children against the development of asthma; next steps are to investigate if dogs also have a beneficial impact when the children are older and have existing disease. This study will provide knowledge needed to help understand disease in underserved dogs in urban neighborhoods, providing data to support keeping dogs and keeping them healthy to benefit both dogs and their owners.

Endocrinology

02488

Addison's Disease and Symmetrical Lupoid Onychodystrophy in Bearded Collies Provide Common Ground for Identifying Susceptibility Loci Underlying Canine Autoimmune Disorders

Principal Investigator: Anita M. Oberbauer, PhD; University of California, Davis

Total Grant Amount: \$118,458

Grant Period: 5/1/2018- 4/30/2020

Project Abstract: Hypoadrenocorticism or Addison's disease (AD) is a life-threatening condition that afflicts multiple dog breeds and results from autoimmune destruction of the adrenal glands. Similarly, another canine autoimmune condition that causes pain and suffering is Symmetrical Lupoid Onychodystrophy (SLO). Both AD and SLO are postulated to be complexly inherited and preliminary data suggest a common set of susceptibility genes working in concert with additional genes that determine expression of either disease. For the study of AD and SLO the investigators will focus on the Bearded Collie breed due to its relatively high prevalence of both conditions and a genomic structure favorable for identifying variations in the DNA. The investigators will scan the entire canine genome using genetic markers coupled with whole genome sequencing to identify chromosomal regions that harbor genetic changes contributing to disease manifestation. The disease risk conferred by each of these genetic variants, or quantitative trait loci (QTL), will then be calculated to develop a tool for selecting sires and dams early in life, thereby allowing breeders to choose mating pairs that will produce offspring with a low likelihood of developing AD and SLO.

New

02428

Identifying the Disease-Defining Autoantibodies in Canine Addison's Disease

Principal Investigator: Steven G. Friedenberg, DVM, PhD; University of Minnesota

Total Grant Amount: \$181,864

Grant Period: 3/1/2018- 8/31/2020

Project Abstract: Addison's disease is a common and life-threatening disorder in dogs in which the body's immune system destroys the outer layer of the adrenal glands. The adrenal glands produce hormones that are critical for energy metabolism, immune system function, intestinal health, and kidney function. Symptoms of Addison's disease can mimic other conditions, and as a result, many dogs remain undiagnosed for years. About one-third of dogs with Addison's disease are diagnosed only after suffering an acute adrenal crisis, which can cause a wide range of complications that require emergency stabilization and hospitalization. Today, there is no way to predict which dogs will develop Addison's disease before they become sick. If such a test were available, veterinarians would be able to evaluate high-risk dogs before they show signs, helping to prevent disease-related complications and potentially enabling earlier treatment. In this study, the investigator will use a novel approach combining gene and protein sequencing to identify the antibodies that target the adrenal glands in Standard Poodles, Portuguese Water Dogs, and English Cocker Spaniels with Addison's disease. These antibodies are produced by the immune system before the onset of clinical signs. The ability to identify these antibodies would therefore provide a test for early diagnosis. This research will contribute to progress in developing an important clinical test for Addison's disease that can help improve the lives of the many dogs at high risk of developing this life-threatening condition.

02417-A

Serum Total Histones in Dogs with Acute Pancreatitis, Their Association with Laboratory Findings, Markers of Inflammation and Outcome: A Prospective Longitudinal Study

Principal Investigator: Ran Nivy, DVM; The Hebrew University of Jerusalem

Total Grant Amount: \$14,200

Grant Period: 12/1/2017- 11/30/2018

Project Abstract: Acute pancreatitis (AP) is a common, potentially fatal, inflammatory disease in dogs. Miniature Schnauzers and several Terrier and Non-sporting breeds are predisposed to develop AP. The spectrum of clinical signs greatly varies, from transient inappetence in mild cases, to intractable gastro-intestinal signs and jaundice in severe ones. The result of aberrant activation of pancreatic digestive enzymes, the ensuing inflammatory reaction within the pancreas and its surrounding tissues induces edema formation and tissue necrosis. In severe cases, inflammation spreads to other organs, leading to hemostatic disturbances, multi-organ dysfunction and ultimately, to death. Several measurable inflammation markers increase in canine pancreatitis. Recently, studies of human and murine AP have demonstrated significant increases in extracellular serum histones. Histones are evolutionally conserved nuclear proteins, constituting the basic structure with which DNA interacts. Histones exert proinflammatory properties, with many deleterious effects on various body cells, and hemostasis. Interestingly, their pernicious effects can be partly or completely abrogated therapeutically (e.g., administering heparin or activated protein C). Recently, circulating histones have shown excellent performance in predicting persistent organ failure and mortality in humans with AP. The investigators will measure, free total serum histones in dogs with naturally occurring AP, and examine their association with other laboratory analytes, and with the prognosis. Should serum histones be found to increase in canine AP, as in humans, this may open up new therapeutic and research avenues for this serious disease.

02366-A

Individualization of Pharmacological Interventions in Diabetic Dogs

Principal Investigator: Nicolas Villarino, Med.Vet.; Washington State University

Total Grant Amount: \$14,435

Grant Period: 5/1/2017- 4/30/2019

Project Abstract: Diabetes mellitus is a disease of middle-aged to older dogs which means many affected dogs will develop other diseases such as arthritis, infections, and behavior disorders, all requiring drug therapy. Poor control of glucose levels in diabetic dogs can alter how drugs behave in the body, which can result in drug toxicities. This is an area of intense investigation in diabetic humans, but such effects have not been investigated in canine medicine, and prescribed treatments may result in individual dogs being under- or overdosed. The investigators intend to move from a 'one dose fits all' strategy to an individualized medical approach to ensure each patient receives optimal pharmacological therapy. Completion of this study is the first step toward establishing an in vitro method for evaluating the many drugs used in diabetic dogs. The long-term goal is to develop a free downloadable application for mobile devices (smartphones and tablets) for use by clinicians to make treatment selection, and to avoid drugs that may cause problems in diabetic patients. This research stands to play a substantial role in the clinical management of dogs with diabetes mellitus.

02342-A

Molecular Analysis of Giant Schnauzer-Type Congenital Hypothyroidism

Principal Investigator: John C. Fyfe, DVM, PhD; Michigan State University

Total Grant Amount: \$14,900

Grant Period: 6/1/2017- 5/31/2019

Project Abstract: Isolated congenital hypothyroidism (CH) is a condition occurring at or near birth characterized by insufficient thyroid hormone production. The disorder in purebred dogs is usually inherited and leads to dwarfism and mental dullness. CH in Giant Schnauzers (GS) was first described in 1991 (Greco, et al) as a likely autosomal recessive disorder due to failed activity of the hypothalamus or pituitary gland. Since then the investigators have studied GS CH in three widely separated families and found pituitary failure of thyroid stimulating hormone (TSH) production beginning at birth in most affected dogs, but not until several months of age in a few. They mapped the genetic locus to a region of dog chromosome 28. The researchers will now perform DNA sequencing experiments of affected dogs and their parents and candidate variants will be assessed further by Sanger sequencing in all available members of the three families, as well as a large number of GS DNA samples available in the OFA CHIC repository. A successful outcome will lead to a reliable genetic test for GS CH, increased understanding of an essential pituitary function, and illumination of a highly similar condition reported in Miniature Schnauzers.

Epilepsy Initiative

02323

Efficacy of Cannabidiol (CBD) for the Treatment of Canine Epilepsy

Principal Investigator: Stephanie McGrath, DVM, MS; Colorado State University

Total Grant Amount: \$356,022

Grant Period: 12/1/2017- 11/30/2020

Project Abstract: Epilepsy is the most common neurologic condition in dogs. Approximately 20-30% of dogs receiving standard therapy remain uncontrolled for their seizures. Additionally, the side effects of the antiepileptic drugs (AED) are often unacceptable. Thus, there is a need for an AED that is efficacious with minimal side effects. Cannabidiol (CBD), a prominent non-psychoactive component of the Cannabis sativa plant, has been shown to have anti-convulsant properties. While CBD offers promise as a treatment for canine epilepsy, controlled studies are needed to prove its effectiveness. In this randomized, double-blinded, placebo-controlled, crossover clinical trial, client-owned dogs with uncontrolled epilepsy will be enrolled following a full seizure evaluation, including bloodwork and magnetic resonance imaging. The canine patients will first receive either a placebo or CBD in addition to their standard AED protocol and then the opposite drug in this crossover designed study. Seizure frequency and medication side effects will be monitored by owners using a seizure log and questionnaire. Regular CBD plasma concentrations, routine bloodwork and serial physical examinations will be monitored by the investigator. The primary goal of the study is to determine the efficacy of CBD in the treatment of canine epilepsy. If CBD is effective in decreasing seizure frequency, it has the potential to improve the quality and length of life for dogs with uncontrolled epilepsy, and add a much-needed tool for veterinarians in the treatment of canine epilepsy.

02252

Investigating a Ketogenic Medium-Chain Triglyceride (MCT) Supplement for the Treatment of Drug-Resistant Canine Idiopathic Epilepsy and Its Behavioral Comorbidities

Principal Investigator: Holger Andreas Volk, DVM, PhD; Royal Veterinary College, University of London

Total Grant Amount: \$107,697

Grant Period: 5/1/2016– 9/30/2018

Project Abstract: Canine epilepsy is a chronic neurological condition, often requiring lifelong medication with anti-epileptic drugs (AEDs). Despite appropriate treatment with available AEDs, seizure freedom may not always be achievable. Indeed, over two-thirds of dogs with epilepsy continue to have seizures long-term and around 20-30% remain poorly controlled on standard AEDs. The hardest to treat dogs are termed 'refractory' or 'drug-resistant' patients. There is an urgent need to develop alternative treatments to improve the quality of life (QoL) of drug-resistant patients. The ketogenic diet, originally characterized as high in fat and low in carbohydrates, has been a successful treatment in children with epilepsy for several decades, decreasing seizure activity and even leading to seizure freedom in drug-resistant patients. Recent research has identified that a component of the ketogenic diet, a medium-chain fatty acid (MCT) called C10 has direct anti-seizure effects on the brain. The investigators will assess whether dietary supplementation with ACT oil containing C10 for dogs with drug-resistant epilepsy will reduce seizure frequency and/or severity. As epilepsy has multiple impacts on QoL beyond seizure frequency, the researchers will also investigate whether the MCT supplement alters the side effect profile of AEDs, improves behavioral problems associated with epilepsy (e.g. anxiety) and cognition, and improves the stress levels of the affected dog. If successful, MCT supplements could provide a new tool for canine epilepsy treatment.

Gastrointestinal Disease

02523-MOU

Identifying the Genetic Basis of Protein Losing Enteropathy in Yorkshire Terriers

Principal Investigator: Kenneth W. Simpson, BVMS, PhD; Cornell University

Total Grant Amount: \$46,440

Grant Period: 3/1/2018- 2/29/2020

Project Abstract: Chronic intestinal disease associated with the loss of protein into the gut, termed protein losing enteropathy (PLE), is a severe, life threatening condition that affects many dog breeds, including the Yorkshire Terrier, Soft-coated Wheaten Terrier, Basenji, Norwegian Lundehund, and Chinese Shar-pei. The syndrome of PLE is most common in Yorkshire Terriers (4.2-10 fold relative risk), and affected dogs frequently suffer from severe weight loss, accumulation of fluid within tissues and body cavities, diarrhea, low levels of circulating proteins, increased risk for abnormal clotting, and derangements in vitamin and mineral homeostasis. The microscopic appearance of the small intestine of Yorkshire Terriers with PLE (YT-PLE) is distinct from PLE in other breeds, suggesting it is caused by a breed-specific genetic abnormality. Despite aggressive treatment, remission is variably achieved and relapse is common. Long-term survival is infrequent with recent studies indicating treatment failure in approximately 50% of Yorkshire Terriers with PLE. The high morbidity and mortality of YT-PLE indicates the desire to eradicate this disease through breeding practices. The investigators are seeking to identify genetic regions and genes associated with YT-PLE to enable prevention of this disease, provide insights into the development of PLE across species, and facilitate the discovery of more specific and effective therapies. Preliminary studies in their laboratory have linked several genetic regions to YT-PLE but additional genotyping of DNA samples from YT with and without PLE is required to enable definitive identification of causal abnormalities. *Funding for the research is provided through the efforts and generosity of the Yorkshire Terrier Club of America and the Yorkshire Terrier Club of America Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

02338

The Genetics of Bloat in German Shepherd Dogs: The Roles of Immune System Genes and the Gut Microbiome

Principal Investigator: Michael Alan Harkey, PhD; Fred Hutchinson Cancer Research Center

Total Grant Amount: \$152,270

Grant Period: 6/1/2017- 5/31/2019

Project Abstract: While gastric dilatation-volvulus (GDV or bloat) is a serious problem for many large canine breeds, little is known about the causes of this deadly disease. The most significant factors may be genetic, since certain breeds are more susceptible than others, and strong familial predispositions are seen within breeds. The investigators have recently shown a significant association of three immune genes with bloat in Great Danes. For each of the three genes, one allele (variant) is found at unusually high frequency in dogs that have been treated for bloat, and the presence of any one of these "risk" alleles triples the chance that the dog will experience bloat at some time in its life. The research team also showed that the bacterial population living in the gut (the gut microbiome) is altered in dogs with bloat, and in dogs that carry these "risk" alleles, which may predispose these dogs to bloat. It is not known if other breeds show this same association of genetics and microbiome with bloat. The team will investigate whether bloat in German Shepherd Dogs is associated with the same risk alleles and the same microbiome profiles as were seen in Great Danes. The results of this work could lead to genetic tests for at-risk dogs, as well as dietary or probiotic therapies to prevent bloat.

01937

Evaluating the Complex Genetic Basis of Bloat

Principal Investigator: Elizabeth A. Rozanski, DVM; Tufts University

Total Grant Amount: \$251,097

Grant Period: 1/1/2014- 12/31/2018

Project Abstract: Gastric dilatation-volvulus (GDV), or bloat, is a common condition in large and giant breed dogs with an unacceptably high morbidity and mortality rate. Due to the importance of GDV in many dog breeds, several previous studies have investigated potential risk factors for the development of GDV. It is known that there is no single cause for GDV, rather its occurrence is multifactorial, with both genetic and environmental factors likely contributing. This study will allow for further investigation of how these risk factors cause GDV through the application of genomic and molecular methods. Samples from purebred dogs with GDV will be analyzed and compared to control dogs of similar age and breed that have not developed GDV. A genome wide association study (GWAS) will help to identify differences in the genetic makeup of dogs with GDV, and see which genes are turned on and off in GDV (epigenomics). The study will also determine if dogs with GDV have different types or amounts of proteins, hormones and other molecules in their blood and tissues (transcriptomics, proteomics and metabolomics). The investigators hypothesize that only when all of this information is considered together (genomic, epigenomic, transcriptomic, proteomic and metabolomic) will we truly understand what causes GDV, and guide more effective preventive and treatment strategies.

General Canine Health

02529

Understanding the Genetics of Adverse Drug Reactions in Sighthounds: Phase II

Principal Investigator: Michael H. Court, BVSc, PhD; Washington State University

Total Grant Amount: \$172,765

Grant Period: 6/1/2018- 5/31/2020

Project Abstract: Life-threatening unanticipated reactions to drugs with a narrow margin of safety, such as those used for anesthesia and to treat cancer, are a common yet serious concern for dog owners and veterinarians. Investigators at Washington State University have been conducting research to identify the cause of extremely slow recovery from anesthesia in a high proportion of Greyhounds, as well as in other sighthound breed dogs, including Italian Greyhounds, Scottish Deerhounds, Borzois, Irish Wolfhounds, Salukis, Afghan Hounds, and Whippets (among others). In previous work funded by the AKC Canine Health Foundation (#02242), the investigators discovered several mutations that were shown by cell-based testing to significantly decrease the function of genes responsible for breaking down (metabolizing) commonly used anesthetic drugs, as well as many other drugs used in dogs. The goal of this next phase of research is to develop a novel drug sensitivity test using saliva, blood or urine samples to identify dogs within a breed (or specific breeds) that metabolize drugs very slowly, thus creating a "personalized" or individual dog approach to drug selection. This test will then be used to confirm that the identified gene mutations are the cause of slow drug metabolism in sighthound dog breeds – as well as identify other breeds and individual dogs that could suffer from similar adverse drug reactions.

New

02475-A

New

Effect of Periodontal Treatment on Glycemic Control in Canine Diabetic Patients: A Prospective, Clinical Study

Principal Investigator: Michal Mazaki-Tovi, DVM; The Hebrew University of Jerusalem

Total Grant Amount: \$14,970

Grant Period: 5/1/2018- 4/30/2019

Project Abstract: Diabetes mellitus (DM) is a common endocrine disorder in dogs, with a strong breed disposition. The disease is associated with significant morbidity and death when left untreated, and tight control of blood glucose levels is crucial in avoiding the harmful effects of long-standing hyperglycemia. Insulin administration, appropriate diet, and treatment of concurrent diseases which interfere with insulin actions constitute the cornerstones of treatment. Among the various diseases in humans which affect treatment success, periodontal disease (PD) adversely affects glycemic control, and periodontal treatment leads to improvement in diabetic control. Periodontal disease is a multi-factorial, bacterial disease of dental supporting tissues. A common occurrence in dogs, its incidence increases with age, and most dogs over the age of five are afflicted by PD to variable extent. Beyond the local consequences of PD on dental and gingival health, PD induces a systemic inflammatory reaction, which purportedly accounts for its detrimental effects on diabetic control. In veterinary medicine, only few case reports and small experimental studies, involving 1 to 4 dogs, investigated the role of periodontal treatment (PT) on diabetic control. This study will investigate the effects of PT on diabetic control in a larger cohort of dogs through a prospective, clinical study. The investigators will also examine possible associations between PT, diabetic control and markers of systemic inflammation to elucidate possible mechanisms which may shed light on the relationship between the two conditions.

02434-A

Characterization of the Anal Sac Microbiota in Dogs with Sacculitis

Principal Investigator: Marcio Costa, DVM, PhD; University of Montreal

Total Grant Amount: \$14,709

Grant Period: 12/1/2017- 11/30/2019

Project Abstract: Anal sacs are two small cavities found adjacent to the anus in dogs, and accumulate secretions from the ad-anal glands. Inflammation of the anal sac (sacculitis) is a frequent condition affecting up to 12% of dogs and is mainly caused by bacterial infection. Therefore, treatment of this disease requires antibiotics, but reoccurrence can occur and often culminates with surgery. During the last decades, the development of new methods for DNA sequencing has allowed a better characterization of bacterial communities, since only the minority of those organisms grow in culture media. Imbalances of the normal populations are related to predisposition to certain diseases. Risk factors for sacculitis in dogs are still uncertain, but studies investigating the role of bacteria in this disease are rare. The investigators will characterize the microbiota present in the anal sac of dogs affected by sacculitis and compare it to the healthy contra-lateral sac using next generation DNA sequencing (NGS). In addition, factors such as antibiotic use, severity of inflammation and clinical response to treatment will be followed. Understanding the physiopathology of sacculitis in dogs may lead to increased success rates following conservative treatment, reducing the need for invasive surgery.

02353-A

Characterization of Naturally-Occurring Neuropathic Pain in Dogs

Principal Investigator: Paulo V. Steagall, DVM, MSc, PhD; University of Montreal

Total Grant Amount: \$14,753

Grant Period: 11/1/2017- 10/31/2018

Project Abstract: Clinical experience demonstrates that canine patients commonly suffer from neuropathic pain and little is known to address this issue. The researchers will investigate different tools for the recognition, diagnosis and treatment of neuropathic pain using a multidisciplinary approach. A two-phased study will include client-owned healthy dogs as controls and dogs with naturally-occurring neuropathic pain (Neuropathic Group-NG). In a prospective, randomized, masked clinical trial using appropriate inclusion and exclusion criteria, dogs in the NG group will be assigned to receive treatment with a drug for neuropathic pain (gabapentin), or gabapentin in combination with an anti-inflammatory drug (meloxicam) in a cross-over design (dogs will receive both treatments during the study). Placebo will be administered between treatments to assess placebo effect; additional analgesics will be administered if needed. Quality of life, pain scores, client-specific outcome measures, biomarkers of inflammation and quantitative sensory testing will be evaluated and compared with controls for observation of treatment effect, and blood concentrations of gabapentin will be measured. This multidisciplinary research may have a timely, immediate impact in veterinary medicine, canine health and welfare by providing important insight into diagnosis and therapeutic options for neuropathic pain.

02322

Analysis of the Health, Behavioral, and Longevity Data Collected in the 9/11 Medical Surveillance Longitudinal Study

Principal Investigator: Cynthia M. Otto, DVM, PhD; University of Pennsylvania

Total Grant Amount: \$37,672

Grant Period: 2/1/2017- 1/31/2019

Project Abstract: Following the attacks of September 11, 2001 on the World Trade Center and Pentagon, the AKC Canine Health Foundation awarded funds to the only lifetime longitudinal study tracking the medical and behavioral impacts of a major national disaster on the health and behavior of search & rescue (SAR) dogs. On June 6, 2016, the last study dog was laid to rest and data collection for the 9/11 Medical Surveillance Study was concluded. With 15 years of data, including annual radiographs, bloodwork, and handler surveys (health, performance, and behavior), the opportunity for in-depth analysis and discovery of new best practices and protocols for SAR dogs has never been greater. Data collected from deployed dogs will be compared to data collected from control SAR dogs that underwent similar training and careers, but did not deploy to 9/11. The investigators will explore three key areas of data: behavior, occupational hazards, and longevity related to health and work. Critical information gleaned from this study will have major implications applicable to the development, training, and care of our nation's SAR dogs, other working canines, and even companion dogs. Results will improve our understanding of traits of successful SAR dogs and thus influence dog selection. Importantly, following characterization of trait heritability, this data could be critical to a focused breeding program. The complete analysis of the occupational hazards of SAR dogs will shape preventive practices to allow these dogs to safely and effectively fulfill their mission of saving human lives.

02235-A

Medical Surveillance of Dogs Deployed to the World Trade Center and the Pentagon on 9/11/01

Principal Investigator: Cynthia M. Otto, DVM, PhD; University of Pennsylvania

Total Grant Amount: \$11,340

Grant Period: 12/1/2015- 12/31/2018

Project Abstract: As the investigators wrap up the 14th year of the 9/11 Medical Surveillance Study, they continue to follow 2 surviving deployed dogs and 1 surviving control dog, each of them now 16 years of age. The initial study group consisted of 95 deployed and 55 non-deployed Search and Rescue dogs. Findings to date indicate that overall these dogs have demonstrated good longevity and quality of life. This final phase of the study will monitor the remaining dogs, placing emphasis on health issues occurring in later years of life and necropsy evaluations at time of death. This vital information will allow for a comprehensive understanding of the impact of the deployment and a life spent working Search and Rescue on long-term canine health. The rate of cancer in deceased deployed dogs to date is not different than in deceased control dogs. Of note, within the deployed dogs, the median age at death was significantly lower for dogs with cancer than the non-cancer group; however, this was not the case with the control group. As the final three dogs approach the end of their natural lives, the investigators will further define any effects of the 9/11 deployment in the full cohort of study dogs. As they analyze the data, a full picture of causes of death and types and incidences of cancer, and long-term impacts of the 9/11 deployment may become clear. The ability to see this study through to completion and publish the long-term findings will provide critical information to canine health that may affect future tactics employed in Search and Rescue missions. *The AKC Canine Health Foundation is proud to have funded Dr. Otto through all 17 years of this important work for Search and Rescue dogs from its inception in 2001.*

Hepatic Disease

02363-A

Platelet Function in Dogs with Chronic Liver Disease

Principal Investigator: David L. Panciera, DVM, MS; Virginia-Maryland Regional College of Veterinary Medicine

Total Grant Amount: \$14,904

Grant Period: 6/1/2017– 12/31/2018

Project Abstract: Chronic liver disease is common among adult dogs with numerous breeds being predisposed. Liver biopsy is usually required to identify the underlying cause of liver disease in these patients, and is often recommended to monitor response to treatment. Because dogs with liver disease have abnormal clotting activity, bleeding is a substantial risk of biopsy. Routine screening for clotting abnormalities in dogs with liver disease is accomplished using blood tests including prothrombin time, partial thromboplastin time, and platelet count. Unfortunately, these routine tests do not necessarily correlate with excessive biopsy-induced bleeding, which makes predicting and preventing hemorrhage during liver biopsy difficult. Humans with liver disease have abnormal platelet function that contributes to abnormal coagulation. Because standard diagnostics do not assess platelet function, we propose to evaluate platelet function in dogs with chronic liver disease. The investigators will determine if dogs with chronic liver disease have platelet dysfunction and if there is a correlation between platelet function and bleeding after liver biopsy. The research team will use two methods to evaluate platelet function in canine patients with chronic liver disease undergoing ultrasound-guided liver biopsies to determine if there is a relationship between platelet function and hemorrhage after biopsy.

02297-MOU

Understanding the Genetics of Hepatic Copper Toxicosis in the Dalmatian

Principal Investigator: Andrew Lawrence Mason, PhD; University of Alberta

Total Grant Amount: \$100,000

Grant Period: 3/1/2017- 2/28/2019

Project Abstract: Copper toxicosis, leading to early death from liver disease, was first described in Bedlington Terriers in 1975, with similar diseases described in other dog breeds including the Labrador Retriever, West Highland White Terrier, Skye Terrier, and Doberman Pinscher. Genes have been linked to copper toxicosis in the Bedlington Terrier and the Labrador Retriever, but the genes differ by breed. In most breeds the genes are not known. Copper toxicosis was considered rare in the Dalmatian but may be more common than previously believed. Symptomatic dogs may be misdiagnosed as having other liver diseases, never appropriately diagnosed or only diagnosed with copper overload at a terminal stage. The investigators aim to identify the faulty gene(s) in Dalmatians using an advanced whole genome sequencing strategy to obtain the genome sequences of carefully selected members of an affected Dalmatian pedigree. Identification of the problem gene is the first step towards genetic testing and to improved breeding practices necessary to eradicate hepatic copper toxicosis from the Dalmatian breed. Gene identification will help raise awareness of copper toxicosis in the Dalmatian breed, lead to more rapid diagnosis of the condition, and support the search for the most effective therapy. *Funding for the research is provided through the efforts and generosity of the Dalmatian Club of America and Dalmatian Club of America Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

01986

Profiling the Metabolic and Lipid Imbalances that are Causative of Gallbladder Disease in Dogs

Principal Investigator: Jody L. Gookin, DVM, PhD; North Carolina State University

Total Grant Amount: \$135,354

Grant Period: 1/1/2014- 12/31/2018

Project Abstract: The gallbladder mucocele (GBM) is one of the most common, poorly understood and deadliest biliary diseases of dogs. A GBM develops when the gallbladder secretes abnormal mucus that eventually obstructs or ruptures the gallbladder. GBM formation afflicts all dogs, but especially Shetland Sheepdogs, Miniature Schnauzers and Cocker Spaniels, and in general, dogs with disorders of steroid hormone or lipid metabolism. By the time a diagnosis of GBM is made, emergency surgery to remove the gallbladder is often required. After surgery, only 22-50% of dogs survive to be discharged from the hospital. There is a critical need to determine why dogs form a GBM so we can prevent the high cost and lost lives of these dogs. Based on the breeds and diseases that predispose to GBM, Dr. Gookin hypothesizes these dogs have a unique disturbance in cholesterol or lipid metabolism. If the cause of this disturbance can be identified then the investigators will be able to understand why GBM form, develop tests for early diagnosis and design diets or drugs to prevent GBM formation.

Immunology and Infectious Disease

02532-A

New

Canine Influenza: Occurrence, Spatial and Temporal Trends and Identifying Modifiable Factors to Reduce Transmission at Events in the United States

Principal Investigator: J. Scott Weese, DVM; University of Guelph; Jason Stull, VMD, MPVM, PhD; Ohio State University and University of Prince Edward Island

Total Grant Amount: \$14,040

Grant Period: 6/1/2018- 2/28/2019

Project Abstract: Canine influenza is an important disease affecting dogs, especially in situations where many dogs come together (e.g., boarding, dog shows, doggie daycare). Several recent outbreaks of canine influenza have been reported in the United States with anecdotally high levels of dog-dog transmission of canine influenza virus (CIV), resulting in dog illness and death as well as disruption or cancellation of shows and other events. Despite the importance of this disease, little is known of modifiable factors linked to CIV spread in dogs. Work to address this research gap is greatly needed in order to answer key questions about CIV and future control and prevention needs. The investigators will utilize an existing database of dogs tested for CIV to determine any recent changes over time and region (outbreaks) of CIV in the United States. Surveys of dog show participants will also be used to collect information on dog, owner/handler, and canine event factors related to CIV spread. Results will be used to develop and pilot a voluntary surveillance network to serve as an early warning mechanism to identify disease outbreaks (CIV and others) linked to dog events. Findings from this work will allow for targeted prevention strategies to reduce CIV spread in the United States which could be applied to other canine infectious diseases.

02461-A

Innate Immune Response to *Leptospira* in Naturally Exposed Dogs

Principal Investigator: Sreekumari Rajeev, BVSc, PhD; Ross University School of Veterinary Medicine

Total Grant Amount: \$15,000

Grant Period: 12/1/2017- 11/30/2018

Project Abstract: Leptospirosis is a zoonotic disease of global occurrence and may result in life threatening illness in animals and humans. *Leptospira* may also reside in the kidney of many animal species including dogs without causing disease. Factors predisposing to clinical disease, carrier stage, or protection needs to be clarified. Dog are susceptible to fatal illness and at the same time may serve as asymptomatic reservoirs. Protection from vaccines is short-lived and suboptimal. Information available on immune response in naturally infected dogs is sparse. The investigators hope to unravel the host and pathogen factors in *Leptospira* infection that leads to fatal disease, chronic asymptomatic infection, or bacterial clearance. Innate immune cells are the first line of defense against *Leptospira* infection, initial experiments will determine the response of innate immune cells of dogs. The knowledge acquired from this study will be beneficial for the development of control and treatment strategies for this problematic and life-threatening disease. As leptospirosis is a zoonotic disease where animal, human and environmental interface is essential for transmission, the findings from this study will have a One Health impact.

02458-A

A Laboratory Test for Detecting Drug Resistance in Canine Heartworm Disease

Principal Investigator: Matthew Brewer, DVM, PhD; Iowa State University

Total Grant Amount: \$15,000

Grant Period: 2/1/2018- 1/31/2019

Project Abstract: *Dirofilaria immitis* is the nematode parasite that causes heartworm disease in the United States. Heartworm infection causes severe pathology and suffering in dogs and cats. Until recently, heartworm infection was a preventable disease due to the availability of effective monthly preventative treatments. A recent development shows drug-resistant heartworms have emerged in the United States. The scope of the resistance issue has not yet been characterized because there is a critical need to develop a test that can discriminate drug-susceptible and drug-resistant parasites. Recent research assessed computer-aided motility studies of the parasite in the presence of drugs, however, there are not motility differences among parasite isolates in these assays. The investigators have developed biochemical stains and measurements that can quantify parasite killing in the presence of antiparasitic drugs. In this study, the investigators will evaluate various metabolic assays and staining procedures to compare drug-susceptible and drug-resistant heartworm isolates in an effort to identify the best assay for detecting heartworm killing, and thereby creating a tool to rapidly identify resistant infections in dogs.

02448

Canine Chagas Disease: Characterizing Cardiac Abnormalities, Vector Infection and Control Strategies, and Parasite Strains in Kennel Environments

Principal Investigator: Sarah A. Hamer, DVM, PhD; Texas A&M AgriLife Research

Total Grant Amount: \$160,407

Grant Period: 1/1/2018- 12/31/2019

Project Abstract: Chagas disease is a parasitic infection that can cause acute death and chronic heart disease in any breed of dog, and there is no vaccination or approved treatment. There is currently an unprecedented recognition for canine Chagas disease in the southern US, where infected kissing bug vectors occur. The disease is well-studied in Latin America but the current lack of knowledge about canine infection in the US hinders our ability to protect canine health. Infected dogs occur across the range of kissing bugs in the southern half of the US, and Texas is a particular hotspot for infection due to the diversity of kissing bugs and high parasite infection prevalence. The investigators will establish a network of AKC breeding kennels in four key areas representing range limits of different vector species to: (1) characterize heart abnormalities of infected dogs using ECG and cardiac troponin I, a non-invasive biomarker of cardiac injury; (2) collect kissing bugs from kennel environments using complementary methods including a trained bug scent detection dog to determine vector infection prevalence and blood meal sources; and (3) characterize parasite strains in dogs and vectors because different genetic variants of the parasite are associated with different disease outcomes. Importantly, because this zoonotic disease is an emerging public health threat to canine owners and the veterinary community, the discoveries made will help to simultaneously advance both canine and human health initiatives.

02441

Evaluation of a New Vaccine for Canine Brucellosis

Principal Investigator: Angela M. Arenas, DVM, PhD; Texas A&M AgriLife Research

Total Grant Amount: \$67,524

Grant Period: 3/1/2018- 2/28/2019

Project Abstract: Canine infection by *Brucella* spp. constitutes a serious problem for dog breeders and pet owners, leading to the economic burden associated with reproductive loss and veterinary care. Canine brucellosis is also considered a public health concern because of its potential to be transmitted to humans. Within the US, the disease has reemerged due to the chronic persistence of the organism, low dose for infection, low sensitivity and specificity of the current diagnostic tests, and most importantly, the lack of a protective vaccine for dogs. Historically in the US, brucellosis control efforts for cattle, sheep, goats and domestic pigs have been successful mainly due to the availability of protective and efficacious vaccines. The goal of the proposed research is to develop a brucellosis vaccine that is safe, stable, free of side effects and efficacious for dogs. Previous CHF funding (Grant #02275-A) has permitted the investigators to successfully engineer a promising live attenuated vaccine candidate, denominated B. canis RM666ΔvjbR. This study will further investigate the ability of the vaccine candidate to induce appropriate immunity and will also develop a diagnostic assay capable of differentiating naturally infected vs vaccinated animals, necessary for mass vaccination. The development of a safe and highly protective brucellosis vaccine for dogs will significantly impact owners, breeders and human health by limiting the spread of the disease.

02408

Predicting the Outcome of Coccidioidomycosis in Naturally Infected Dogs

Principal Investigator: Lisa F. Shubitz, DVM; University of Arizona

Total Grant Amount: \$37,129

Grant Period: 3/1/2018- 2/29/2020

Project Abstract: Coccidioidomycosis (Valley Fever) is a systemic fungal infection endemic to the desert southwestern United States. Dogs are affected, with an estimated \$60 million per year in diagnostic and treatment costs. Valley Fever has a variable clinical picture, ranging from subclinical infections to mild disease to severe, uncontrolled disease. Development of a vaccine to prevent, or reduce, illness in dogs is currently underway. T-cells are a type of immune system cell called lymphocytes. It has been demonstrated that a robust T-cell mediated immune response is needed to control the infection in mice and humans. Exploratory work suggests this is also true in dogs. The investigators plan to develop an assay of canine T-cells, from dogs with variable clinical responses to naturally-occurring infections, that will allow them to correlate T-cell responses with the severity of clinical disease. This information will allow better prediction of the clinical course of disease in dogs, resulting in improved treatment recommendations. This assay will also assess the protective response to the vaccine by mimicking the T-cell mediated response seen in dogs with coccidioidomycosis, and will also be applicable to future studies of immune responses to other canine infectious diseases.

02407-A

In vitro Efficacy of Nano-sulfur Against Planktonic and Biofilm State of Resistant Bacteria

Principal Investigator: Domenico Santoro, DVM; University of Florida Health Science Center

Total Grant Amount: \$14,958

Grant Period: 5/1/2018- 4/30/2019

Project Abstract: Antibiotic resistance and biofilm are emerging problems in both human and veterinary medicine. The inappropriate use of antibiotics helps selecting for resistant strains. Biofilms have an increased resistance pattern due to the presence of a shield that hinders penetration of antibiotics. Currently few antimicrobial options are available for resistant bacteria and biofilm causing major concerns for post-surgical patients. Over the past years, the increased development of nanotechnologies has made the fight against bacteria easier and safer due to the use of lower antimicrobial doses, reduced side effects, and increased antimicrobial efficacy. The most commonly used nano-antimicrobial is nano-silver. However, despite its efficacy, worries persist regarding its safety profile and environmental toxicity. Another emerging nano-antimicrobial is nano-sulfur; widely used in the agricultural industry. Sulfur has been a well-known and safe antimicrobial for centuries, however, its efficacy as nano-particles against biofilm formation/disruption is unknown. The investigators will evaluate the efficacy of nano-sulfur against resistant bacteria and in preventing and/or disrupting biofilm on multidrug-resistant Staphylococci (*S. aureus* and *S. pseudintermedius*) and *Pseudomonas aeruginosa*. This study will determine: 1) whether nano-sulfur is effective against bacterial growth and biofilm adhesion/formation/disruption; 2) if nano-sulfur is cytotoxic at antimicrobial concentrations. If proven effective, nano-sulfur will provide a more cost effective and safer treatment for antibiotic-resistance and biofilms.

New

02404-A

The Impact of Lidocaine Administration on Natural Killer Cell Populations in Canine Sepsis

Principal Investigator: Mandy L. Wallace, DVM, MS; University of Georgia

Total Grant Amount: \$14,896

Grant Period: 11/1/2017- 4/30/2019

Project Abstract: Sepsis is a life-threatening condition that results from an excessive systemic inflammatory response to infection. This can occur due to infections in various parts of the body including the chest, abdomen, or bloodstream. Dogs and humans with sepsis have up to a 50% mortality rate, with most dying from organ system failure. This high mortality rate has been linked to the dysfunction of several types of immune cells. One of these cell types, Natural Killer (NK) cells, plays a critical role in the killing of bacteria within the body, but their role has not been evaluated in dogs with sepsis. Administration of the local anesthetic lidocaine, a drug that can decrease pain and correct cardiac arrhythmias, has been shown to increase survival in dogs with sepsis. This study seeks 1) to determine the relationship between Natural Killer cell numbers and phenotype in the blood and disease severity in dogs with abdominal sepsis; and 2) to evaluate if the administration of lidocaine during surgery changes NK cell numbers or affects survival rates in dogs with sepsis from abdominal infection.

02380-A

Estimating Prevalence and Identifying Risk Factors for Canine Leptospirosis in North America

Principal Investigator: Thomas Wittum, PhD; Ohio State University; Jason Stull, VMD, MPVM, PhD; Ohio State University and University of Prince Edward Island

Total Grant Amount: \$14,990

Grant Period: 5/1/2017- 10/31/2018

Project Abstract: Leptospirosis is an important and re-emerging disease of dogs, humans and other species that is transmitted by contact with infected urine. Infected dogs can develop severe illness, including death. Despite being recognized as a disease that appears to be increasing in frequency in dogs across the United States and Canada, many areas important to dog health are unknown. Regions of greatest canine leptospirosis risk, dog factors that increase risk and the most important prevention methods remain unclear. The investigators will use an existing large international database of dogs to determine the occurrence and changes over time and region of this disease. Current "hot spots" for canine leptospirosis will be determined. These "hot spots" will be further evaluated in detail by enrolling dogs and their owners in a follow-up study component to identify key behaviors and practices that can be used to successfully reduce the risk of leptospirosis in dogs. Maps will be created for use by dog owners and veterinarians to identify areas of greatest risk and concern for this disease. Together, maps and risk reduction data will allow for targeted education to individuals with dogs living or traveling to higher-risk areas to protect dogs against leptospirosis.

02245-MOU

Genetic Predisposition to Avian Tuberculosis in Miniature Schnauzers and Basset Hounds

Principal Investigator: Urs Giger, DVM, PhD; University of Pennsylvania

Total Grant Amount: \$106,858

Grant Period: 5/1/2016– 10/31/2018

Project Abstract: While people and dogs are generally resistant to avian tuberculosis (*Mycobacterium avium*) infections, there are certain individuals that lack proper host defense against these intracellular bacteria. The precise molecular basis is still unknown, but there is much interest because of the major morbidity and mortality in susceptible patients. The investigators have recognized that many young adult Miniature Schnauzers (and few Basset Hounds) succumb to systemic avian tuberculosis (referred to as *Mycobacterium avium* complex or MAC), characterized by enlarged lymph nodes, fever, diarrhea and respiratory signs. Based upon pedigree analysis, this appears to be a simple autosomal recessive trait. Preliminary pedigree and limited molecular genetic data suggest a strong signal for one specific small chromosomal region, which the investigators will substantiate using further samples and whole genome sequencing. Identification of the molecular basis of this genetic predisposition will allow for a better understanding of the disease and the development of a DNA screening test to identify animals at risk as well as carriers, thereby reducing the production of dogs predisposed to this fatal disease in future generations. As avian tuberculosis is a zoonotic disease, the findings should provide insight into genetic determinants of host microbe interaction and resistance in dogs and people, and thereby could have an impact on comparative medicine.

Funding for the research is provided through the efforts and generosity of the American Miniature Schnauzer Club. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.

Kidney and Urological Disease

02437-MOU

Characterization of Renal Disease in American Boxer Dogs

Principal Investigator: Jessica Anne Hokamp, DVM, PhD; Ohio State University

Total Grant Amount: \$56,694

Grant Period: 3/1/2018- 2/29/2020

Project Abstract: Chronic kidney disease (CKD) is often a progressive and fatal disease in dogs. Boxer dogs appear to have a predisposition for development of CKD, suggesting that kidney disease in this breed might be heritable. Studies in Europe report an increased frequency of Boxers with kidney and urinary tract maldevelopments leading to CKD, termed "juvenile nephropathy". The investigators' International Veterinary Renal Pathology Service (IVRPS) recently found that juvenile nephropathies are a main underlying cause of CKD in young Boxer dogs; however, there are no published studies that have determined the predominant cause(s) of CKD in Boxer dogs in the United States. The investigators hypothesize that pedigreed Boxers in the U.S. may be afflicted by several causes of CKD, including but not exclusive to juvenile nephropathies. To assess the most common causes of CKD in Boxers, the investigators will perform detailed examination of medical records and archived tissue samples to retrospectively reveal the predominant cause(s) and prevalence of kidney disease in Boxers, and will also prospectively collect and analyze tissue and fluid samples from pedigreed families of Boxers afflicted by the predominant types of kidney diseases. This work will determine if certain types of kidney disease in Boxers follow a heritable pattern and might be related to genetic mutations, allowing for future studies on genetic analysis if an inheritance pattern of disease is determined. *Funding for the research is provided through the efforts and generosity of the American Boxer Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

02263-MOU

Characterization of Kidney Disease in Dalmatians

Principal Investigator: Rachel E. Cianciolo, VMD, PhD; Ohio State University

Total Grant Amount: \$31,434

Grant Period: 5/1/2016- 4/30/2019

Project Abstract: Chronic kidney disease is a significant progressive problem in dogs. Two different hereditary diseases of the urinary system are being studied in Dalmatian dogs: urinary stone formation (urolithiasis) and glomerular disease. These diseases cause distinct clinical signs: urolithiasis leads to urinary tract obstruction while glomerular disease results in protein loss into the urine (proteinuria). The genetic cause of urolithiasis is known while the genetic cause of glomerular disease has not yet been identified. Although one specific type of glomerular disease has been reported in the literature, preliminary investigations indicate that there may be multiple causes of proteinuria in Dalmatians. Evaluation of kidney tissue by the International Veterinary Renal Pathology Service has revealed diverse types of glomerular diseases in Dalmatians, at least 4 of which might be hereditary. Therefore, the most common disease type is unknown and must be identified and characterized. A detailed review of autopsy and biopsy sample archives previously obtained from Dalmatians with proteinuria will be performed. Next, prospective examination of select kidney samples using advanced techniques (electron microscopy and immunofluorescence) will ensure an accurate diagnosis of the glomerular disease. Ultimately, genetic analyses could be performed on related dogs that demonstrate similar glomerular lesions to identify candidate genes. *Funding for the research is provided through the efforts and generosity of the Dalmatian Club of America and Dalmatian Club of America Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

02152

Translation of MicroRNA into an Early Diagnostic Test for Chronic Kidney Disease

Principal Investigator: Mary B. Nabity, DVM, PhD; Texas A&M AgriLife Research

Total Grant Amount: \$26,988

Grant Period: 1/1/2015- 12/31/2018

Project Abstract: Chronic kidney disease (CKD) is a significant cause of illness and death in dogs and is often due to glomerular diseases. Dogs with glomerular disease often have poor outcomes with standard therapy, and specific treatment recommendations are difficult without performing a kidney biopsy to determine the type of glomerular disease present since treatment and outcome among these diseases differ substantially. Even then, there is not understanding of the mechanisms driving these diseases, limiting the ability to optimally treat these dogs. Therefore, tests to non-invasively diagnosis the type of glomerular disease would help veterinarians more appropriately treat these patients and provide insight into the mechanisms that cause the diseases. This could lead to better therapies that slow disease progression and improve quality and length of life in dogs with CKD. One area of emerging importance in CKD is the role of microRNAs (miRNAs) in disease pathogenesis and progression. miRNAs are small molecules that can regulate gene expression by up or down regulation of messenger RNA transcripts and proteins in target tissues. Many studies have found that increases or decreases in miRNAs can serve as biomarkers of diseases, including human CKD. They also contribute to the development of diseases. This work will identify miRNAs in serum and urine of dogs that are specific for the three major causes of glomerular disease in this species. This study will also identify miRNAs associated with disease progression for each of these diseases. Successful completion of these goals will support the translation of miRNAs into diagnostic tests and viable targets for future drug development.

02066

Identification of Novel Biomarkers and Therapeutic Targets for Chronic Kidney Disease in Dogs

Principal Investigator: Mary B. Nabity, DVM, PhD; Texas A&M AgriLife Research

Total Grant Amount: \$108,243

Grant Period: 1/1/2014– 12/31/2018

Project Abstract: Chronic kidney disease is a significant cause of illness and death in dogs. Early treatment can prolong the lives of dogs with chronic kidney disease, but timely detection can be difficult. The outcome for each patient using current, early non-invasive testing is unpredictable. Therefore, improvements in tests to detect kidney damage at an earlier stage would allow veterinarians to provide dogs with appropriate treatments in a more timely fashion to slow disease progression and improve quality and length of life. Further, better treatments are needed to prevent disease progression. MicroRNAs (miRNAs) are small molecules that can regulate gene expression by up or down regulation of messenger RNA transcripts and proteins in target tissues. Many studies have found that increases or decreases in miRNAs can serve as biomarkers of diseases, including human chronic kidney disease. They also contribute to the development of diseases. Dr. Nabity will evaluate miRNAs in the serum and urine of dogs with chronic kidney disease to determine their use as biomarkers of kidney injury and their potential as targets for future therapeutics. They will evaluate kidney tissue, urine, and serum samples from dogs with a hereditary disease that causes early-onset chronic kidney disease, as well as serum and urine from dogs with a variety of other naturally occurring kidney diseases to identify miRNAs that may be useful as biomarkers of kidney damage. Gene and protein targets of altered miRNAs will also be evaluated to learn more about the mechanisms that contribute to the development of chronic kidney disease in dogs.

01844

Treatment of Urinary Incontinence with Multipotent Muscle Cells: A Regenerative Medicine

Approach to a Common Canine Health Problem

Principal Investigator: Shelly Vaden, DVM, PhD; North Carolina State University

Total Grant Amount: \$116,184

Grant Period: 1/1/2013- 12/31/2018

Project Abstract: Urinary incontinence affects more than 20% of spayed female dogs, with medium and large breeds more commonly affected. In the majority of the cases urinary incontinence is caused by dysfunction of the muscles controlling the urethral sphincter. This results in uncontrolled loss of urine and can lead to serious bladder and kidney infections, in addition to irritation and/or ulceration of the skin in contact with the urine. Treatment can include hormone therapy, drugs designed to strengthen the muscle tone of the urethral sphincter, collagen injections, or surgery. Recently, Dr. Vaden's lab has reported that injection of muscle progenitor cells into damaged urethral sphincters can restore normal function in dogs. The purpose of this project is to extend those observations and examine the usefulness of cultured muscle cells for the restoration of function of the urethral sphincter in dogs with naturally occurring urinary incontinence. The effects of the procedure will be determined by owner reported continence scoring, as well as urodynamic testing that will provide an objective measurement for how well the bladder, sphincters, and urethra are storing and releasing urine.

Lung and Respiratory Disease

02507

Characterizing Developmental Lung Disease as a Cause of Sudden Death in the Norwich Terrier

Principal Investigator: Kurt Williams, DVM, PhD; Michigan State University

Total Grant Amount: \$116,076

Grant Period: 3/1/2018- 2/29/2020

Project Abstract: Neonatal respiratory distress syndrome has been attributed to more than 60% of deaths early in life in puppies. The underlying cause(s) of this apparently common problem is poorly understood. Despite the high frequency of respiratory-related mortality in neonatal puppies, there are no reports describing the underlying lung pathology in affected individuals. In human medicine the classification, management and evaluation of diffuse interstitial lung diseases in infants are well described. The most severe neonatal lung diseases in humans develop as a result of abnormal development of the lung, and often result in death soon after delivery. The investigators recently documented microscopic evidence of striking abnormal lung development in puppies of various breeds who died suddenly, suggesting that developmental lung disease (DLD) is an important and unrecognized cause of early death in young puppies. Breeders of Norwich Terriers (NT) report that sudden death of puppies early in life is common. Through preliminary studies, a high incidence of DLD in NT puppies associated with sudden death has been identified. The identification of a breed-association with DLD in the NT presents an opportunity to correlate the pathology and genetics to sudden death in NT puppies. Findings could lead to the development of preventive measures to reduce the incidence of DLD in the NT as well as other dog breeds, and may also be applicable to similar developmental lung diseases in children.

02346-A

Blood Culture and Blood Microbiome as Minimally Invasive Diagnostics for Canine Bacterial Pneumonia

Principal Investigator: Carol R. Reinero, DVM, PhD; University of Missouri

Total Grant Amount: \$11,394

Grant Period: 6/1/2017– 11/30/2018

Project Abstract: Canine bacterial pneumonia is a common and serious respiratory infection. Pneumonia can develop from contagious environmental bacteria or from the dog's own bacteria gaining access to the lungs (e.g. after accidentally inhaling food, liquids or vomit). Diagnosis relies on clinical signs, x-rays, and lung fluid (bronchoalveolar lavage fluid or BALF) analysis. Analysis of BALF helps identify the causative bacteria and aids in appropriate antibiotic selection. While key to definitive diagnosis and management of bacterial pneumonia, collection of BALF requires general anesthesia, which can be especially risky in dogs with severe lung disease. To address the clinical need for a minimally invasive diagnostic test, the first study objective is to determine if blood cultures, acting as a surrogate for BALF analysis, can identify the bacteria causing pneumonia and provide antibiotic susceptibility information. In addition, the investigators will employ molecular means of identification of bacterial populations in samples, so called "microbiome" analysis. Researchers will compare BALF and blood microbiomes to determine sample relatedness and then to the bacteria identified via BALF culture to determine if lung bacteria appear in the blood in minute quantities and whether the predominant cultured bacteria is reflected in the blood microbiome.

Musculoskeletal Conditions and Disease

02400-MOU

Basis of Dwarfism in Great Pyrenees Dogs

Principal Investigator: James R. Mickelson, PhD; University of Minnesota

Total Grant Amount: \$14,915

Grant Period: 1/1/2018- 12/31/2018

Project Abstract: Great Pyrenees dwarfism is not fatal, but is a chondrodysplasia first scientifically described in the mid-1990s. Pups appeared normal at birth, but within two weeks were shorter and smaller than their non-dwarf littermates. This form of dwarfism is not due to hormonal imbalances. Pedigree analysis suggests that it is inherited in an autosomal recessive fashion, and is potentially caused by a single gene. Dogs suspected to be carriers for this condition have normal proportions. The specific underlying genetic cause and the true prevalence of this condition within the breed is unknown. The investigators hypothesize that dwarfism in Great Pyrenees dogs has a genetic basis in which whole genome scans with DNA markers can identify a small chromosomal region that will contain a dwarfism-associated gene, and that high-throughput DNA sequencing will identify the causative mutation(s). The goal is to determine the frequency of the DNA variant in the breed, and to develop and provide a genetic test to inform breeding decisions, and eventually aid in eradicating this disorder from the breed. *Funding for the research is provided through the efforts and generosity of the Great Pyrenees Club of America. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

Neurology

02535-MOU

Clinical and Molecular Genetic Analysis of Juvenile-Onset Laryngeal Paralysis in American Staffordshire Terriers

Principal Investigator: Gary S. Johnson, DVM, PhD; University of Missouri

Total Grant Amount: \$15,000

Grant Period: 7/1/2018- 6/30/2019

Project Abstract:

In this study, the investigators will examine a newly recognized, fatal, neurologic disease referred to as American Staffordshire Terrier juvenile laryngeal paralysis and polyneuropathy (AST-JLPP). This project has two objectives: 1) to conduct thorough neurologic and pathology examinations of affected American Staffordshire Terrier puppies, and 2) to identify the molecular genetic cause for the disease. In the first objective, the neurologic examination will include characterization of the nature and degree of neurological deficits by a board-certified veterinary neurologist. Electromyography (EMG) and various nerve conduction velocities will be measured and recorded, and a laryngeal exam will be performed. Examination of affected nerves and muscle tissue as well as systemic gross and histopathological examination will be performed. A summary of the findings will be published in a scientific veterinary journal so that veterinarians around the world will be able to recognize and diagnose this new disease. To accomplish the second objective, the investigators will perform whole genome sequencing for puppies with AST-JLPP. A genome-wide association study will be used to map the AST-JLPP. Successful discovery of the causal mutation would provide a basis for DNA tests that could be used to confirm a diagnosis of AST-JLPP and aid breeders for marker-based breeding strategies. *Funding for the research is provided through the collaborative efforts and generosity of the Staffordshire Terrier Club of America. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

02470-A

Proteomic Evaluation of Greyhound Meningoencephalitis: A Model for Neuroinflammation in Other Breeds

Principal Investigator: Robert E. Shiel, PhD; University College Dublin

Total Grant Amount: \$10,757

Grant Period: 1/1/2018- 12/31/2018

Project Abstract: Meningoencephalitis is a term used to describe inflammation of the brain and its adjacent membranes, known as meninges. Such neuroinflammatory disorders are common in small animals and can lead to temporary or permanent disability, or death if uncontrolled and progressive. While some neuroinflammatory disorders have a clear bacterial or viral cause, others cannot be identified to a specific infectious cause. Such cases may be true autoimmune diseases, or alternatively, a prior infection may have triggered inappropriate immune system activation with subsequent neuroinflammation long after clearance of an infectious agent. Genetic factors may also play a role, as evidenced by development of specific neuroinflammatory diseases in individual breeds. Although the clinical and pathological features of many canine neuroinflammatory diseases are well-described, there is very limited information available on the underlying causes and pathophysiological processes involved. Greyhound meningoencephalitis is a progressive and invariably fatal neuroinflammatory disorder often affecting multiple littermates. Extensive testing has failed to identify a definitive infectious or genetic cause. The investigators will characterize protein responses within the brain and surrounding fluid in conjunction with previously obtained genetic and transcriptomic data. This approach may allow determination of an underlying cause, and will provide information on the pathways involved to aid understanding of the disease process, and identify potential markers of disease and therapeutic targets.

02452-A

Targeting the T Helper Inflammatory Pathway in Meningoencephalomyelitis of Unknown Origin (MUO)

Principal Investigator: Renee Barber, DVM, PhD; University of Georgia

Total Grant Amount: \$8,845

Grant Period: 1/1/2018- 6/30/2019

Project Abstract: Meningoencephalomyelitis of unknown origin (MUO) is a common neurological disorder of dogs that results in inflammation of the brain and/or spinal cord causing depression, seizures, blindness, difficulty walking, and death. All dogs can be affected but young to middle aged small and toy breed dogs (such as the Chihuahua, Maltese, Pug, and Yorkshire Terrier) are more frequently affected. Currently, brain biopsy is the only means of definitive diagnosis prior to death and the ideal treatment is not known. There is a critical need to improve diagnosis and treatment of MUO. The investigators will identify changes in the immune system associated with inflammation that occurs in the brains and spinal cords of affected dogs, looking for specific products of the immune response, such as interferon-gamma and interleukin 17, in blood and cerebrospinal fluid. Identification of these products could lead to development of new diagnostic tests, strategies for more effective treatment, and improved prognosis prediction.

02387-MOU

Hereditary Deafness in Dogs – Genomic Studies in English Setters Using Full Sibling Pairs

Principal Investigator: George M. Strain, PhD; Louisiana State University

Total Grant Amount: \$12,960

Grant Period: 9/1/2017– 2/28/2019

Project Abstract: Hereditary deafness associated with white pigmentation occurs in several dog breeds. The mechanism of inheritance is unknown, but does not appear to be simple Mendelian. Numerous studies to determine the mode of inheritance and locate the causative gene(s) have thus far failed. The investigators will use a unique modified twin study approach in an effort to determine the mode of inheritance and locate the causative gene(s). Full-sibling littermates will be identified, where one puppy has normal hearing and one is deaf. Like human twins, full siblings should have very similar DNA, which will reduce the variability of the DNA samples when compared to studies of unrelated dogs. The study of pairs of English Setters will be added to an ongoing study examining differences in Dalmatian and Australian Cattle Dog pairs. Identifying candidate deafness genes will be an important breakthrough to understanding deafness in dogs and people, with a goal to establish a genetic test to reduce or eliminate deafness in these canine populations.

Funding for the research is provided through the collaborative efforts and generosity of the English Setter Association of America. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.

02210

Gene Therapy for Canine Degenerative Myelopathy

Principal Investigator: Kathrin Meyer, PhD; The Research Institute at Nationwide Children's Hospital

Total Grant Amount: \$50,000

Grant Period: 1/1/2016- 12/31/2018

Project Abstract: Degenerative myelopathy (DM) is a devastating neurodegenerative disease that affects multiple breeds of dog. DM is an adult-onset disease that manifests at the later stages of life. It is characterized by progressive weakness and inability to control hind limbs, ultimately leading to involvement of forelimbs and complete paralysis. With no current treatments available, euthanasia is the only option available for DM-affected dogs. Recent studies have identified mutation in the Superoxide dismutase 1 (SOD1) gene to be a high risk factor associated with canine DM. In humans, mutations in the same SOD1 gene cause Amyotrophic Lateral Sclerosis (ALS), a neurodegenerative disorder very similar to canine DM. It is also shown that reduction of mutant SOD1 in ALS mouse models provides beneficial effects. Hence, therapeutic approaches to reduce the expression of mutant SOD1 in DM-affected dogs may improve survival and preserve neurologic function. In this study, a viral-based gene therapy approach to treat DM will be evaluated, utilizing Adeno-associated Virus 9 (AAV9) mediated delivery of shRNA to reduce the mutant SOD1 in DM affected dogs. AAV9 is a safe, well tolerated and widely used vector for gene therapy in animals as well as for humans. If successful, this one-time treatment with AAV9 SOD1 shRNA will result in improved quality of life, and significantly extend the survival of dogs affected with this previously hopeless disease.

02172-MOU

Understanding Hereditary Deafness in Dogs

Principal Investigator: George M. Strain, PhD; Louisiana State University

Total Grant Amount: \$120,015

Grant Period: 11/1/2015– 10/31/2018

Project Abstract: Hereditary deafness associated with white pigmentation occurs in numerous dog breeds. The breeds most affected are the Dalmatian (Dal, 22% unilaterally deaf, 8% bilaterally deaf) and the Australian cattle dog (ACD, 11.4% and 3%). The mechanism of inheritance is unknown, and previous studies to determine the mode of inheritance and locate the causative gene(s) have thus far been unsuccessful. Using a modified twin study approach, full-sibling littermates will be clinically and genetically evaluated. Like human twins, full siblings should have very similar DNA, which will reduce the variability of their DNA when compared to studies of unrelated dogs. Using the Illumina CanineHD Beadchip, which contains 172,115 DNA markers (SNPs) spread uniformly across the canine chromosomes, markers will be compared between the sibling pairs, and differences between siblings at individual markers will thus be identified. Using this approach candidate deafness genes can be identified and will advance the current understanding of this heritable disorder. *Funding for the research is provided through the efforts and generosity of the Australian Cattle Dog Health, Education, and Welfare Inc., Australian Cattle Dog Club of America, Dalmatian Club of America, and the Dalmatian Club of America Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

02165-MOU

Identification of Biomarkers and Therapeutic Targets for Canine Degenerative Myelopathy: The Search for a Cure

Principal Investigator: Joan R. Coates, DVM, MS; University of Missouri, Columbia

Total Grant Amount: \$154,077

Grant Period: 1/1/2015- 12/31/2018

Project Abstract: Degenerative myelopathy (DM) is an adult onset disease of the spinal cord causing progressive weakness and paralysis of the hind limbs and eventually all limbs. Mutations in an enzyme that converts superoxide to water and hydrogen peroxide, superoxide dismutase 1 (SOD1), have been linked to DM and amyotrophic lateral sclerosis (ALS-Lou Gehrig's disease). DM is associated with degenerative loss of axons, which transmit signals from the brain and spinal cord to their targets (muscle). Currently no diagnostic test exists that would allow for repeated measurements with minimal invasiveness. Dr. Coates proposes developing a test that would assay the blood and cerebrospinal fluid (CSF) for proteins that are exclusively found in axons under non-disease conditions, referred to as neurofilament proteins. The investigators will correlate the concentrations of neurofilament proteins in CSF and blood with disease stage, and anticipate that neurofilament protein concentration in blood and CSF will increase as disease progresses. Such a test will allow for minimally invasive monitoring of disease. Furthermore, such a diagnostic test could be used to measure the success of therapy, which may be underway in a cohort of DM-affected dogs [Boxers and Pembroke Welsh Corgis (PWC)] (funded by NIH/NINDS). This work will complement the test for neurofilament proteins with other studies that measure disease progression such as specific MRI techniques to evaluate the brain and spinal cord and electrical testing of the muscle and nerves. These are functional disease markers that are also being studied in ALS patients. *Funding for the research is provided through the efforts and generosity of the American Boxer Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee administration of funds and scientific progress reports.*

02162-MOU

Defining The Genetic Foundations of Chiari-Like Malformation and Syringomyelia as a Tool to Better Treat Neuropathic Pain in the Dog

Principal Investigator: Natasha J. Olby, VetMB, PhD; North Carolina State University

Total Grant Amount: \$78,786

Grant Period: 1/1/2015– 12/31/2018

Project Abstract: Chiari-like malformations and syringomyelia (CM/SM) are a common problem in Cavalier King Charles Spaniels (CKCS) causing severe neuropathic pain. The morphometry of the skull has been examined in detail and the development of clinical signs and syringomyelia has been correlated to reduced caudal fossa to cranial cavity volume ratios and stenosis of the jugular foramen respectively. There is evidence this disorder is a complex hereditary trait, but attempts to identify genetic causes have been hampered by assigning an affected or normal phenotype. Use of quantitative data from magnetic resonance imaging (MRI) will allow us to perform a more appropriate genetic analysis of this important and common disease. Quantification of neuropathic pain is challenging and while owners of affected CKCS frequently complain that their pet is experiencing significant pain, a routine evaluation by palpation does not always correlate well to their history. Humans with CM report increased sensitivity to touch and temperature. During case phenotyping for the genetic study, Dr. Olby will also investigate sensory thresholds in affected and normal CKCS to improve the ability to document and treat pain in these patients. This project will define the genetic etiology of this disease with the long-term aim of developing genetic tests for use by breeders, and will quantify the sensory dysfunction experienced by these dogs to facilitate objective therapeutic trials. *Funding for the research is provided through the efforts and generosity of the American Cavalier King Charles Spaniel Club Charitable Trust. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

02157-MOU

Genomics of Deafness in the Dalmatian

Principal Investigator: Claire M. Wade, PhD; University of Sydney

Total Grant Amount: \$120,960

Grant Period: 1/1/2015- 12/31/2018

Project Abstract: Congenital deafness is a health issue that has higher prevalence in certain breeds, including the Dalmatian. Other studies in this breed have found the trait to be inherited in a complex rather than simple Mendelian manner. Using a large number of samples from animals that have been tested for hearing status, Dr. Wade will employ the latest genomic technologies and computational analyses to conduct this study. The ultimate goal is to identify mutations underlying the trait of congenital deafness in the Dalmatian breed and work towards a genetic testing solution for the Dalmatian breeding community. *Funding for the research is provided through the efforts and generosity of the Dalmatian Club of America Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee administration of funds and scientific progress reports.*

Oncology - General

02500

Immune Targeting of the V600E B-Raf Neoantigen in Canine Urothelial Carcinoma

Principal Investigator: Nicola J. Mason, BVetMed, PhD; University of Pennsylvania

Total Grant Amount: \$183,146

Grant Period: 2/1/2018- 1/31/2020

Project Abstract: Bladder cancer or urothelial carcinoma (UC) affects approximately 40,000 dogs per year in the US with specific breeds including Scottish Terriers, West Highland White Terriers, Shetland Sheepdogs, Beagles, and Parson Russell Terriers being over-represented. Affected dogs usually display lower urinary tract clinical signs including bloody urine, frequent urination, difficulty and pain on urinating, and urinary outflow tract obstructions. Standard of care consists of anti-inflammatory drugs either alone or in combination with chemotherapy or radiation therapy. While these treatments can lead to stable disease for 6-12 months, they rarely lead to a cure, and most dogs eventually succumb to their disease. In human medicine, urinary bladder tumors have been shown to exhibit a high gene mutational burden which directly correlates with a favorable response to immune therapies. Canine UC exhibits a similar mutational load suggesting that the disease in dogs may also be immune responsive. In this study, the investigators will evaluate the safety and effectiveness of a novel targeted, immune therapy that aims to promote a powerful immune response against a specific gene mutation (V600E B-Raf) recently identified in up to 87% of dogs with UC. The investigators hypothesize that vaccine-induced anti-tumor immune responses will lead to tumor regression and that such favorable responses will correlate with the baseline mutational burden of the tumor. The investigators will use standard immunological methods and advanced genetic sequencing technology to study systemic and intra-tumoral immune responses to identify biomarkers that may predict immunological and clinical response in dogs.

Collaborative grant between the AKC Canine Health Foundation and the V Foundation for Cancer Research.

02489

Tumor-permissive Collagen Signatures in Canine Mammary Gland Tumors: Development of Prognostic Markers and Targeted Therapies for Improved Outcomes

Principal Investigator: Susan W. Volk, VMD, PhD; University of Pennsylvania

Total Grant Amount: \$162,700

Grant Period: 3/1/2018- 2/29/2020

Project Abstract: Mammary gland tumors (MGT) are the most common malignancies in intact female dogs, and the resulting premature death and morbidity in this sub-population of dogs represents a significant health problem. While genetic alterations within tumor cells can promote their uncontrolled growth and ability to spread to distant sites, recent work indicates that normal, non-malignant cells and extracellular matrix (ECM) within the surrounding tumor stroma also regulate the growth and spread of cancer. The investigators have identified cancer-associated stromal (collagen) signatures in canine MGT biopsy samples that predict clinical outcome better than commonly used markers. These predictive markers may improve the veterinary oncologist's ability to accurately predict which dogs truly need aggressive treatment from those that do not. Notably, their laboratories have shown that inhibition of a collagen-degrading enzyme (Fibroblast Activation Protein (FAP)) and increasing a tumor-suppressive collagen (type III collagen (Col3)) prevent the formation of these tumor-inciting signatures in other species (mouse and human). This work suggests that if these novel targets can suppress tumor-permissive collagen signatures in the dog, we can treat canine MGT more effectively. The goals of this project are 1) to identify additional collagen signatures which predict clinical outcome in dogs, 2) determine how they direct tumor cell behavior and 3) develop therapies that prevent formation of tumor-inciting collagen signatures in canine MGT. Based on the investigators' published and preliminary data, they predict that identifying and targeting tumor-inciting collagen signatures will lead to improvements in both diagnosis and treatment of dogs with malignant MGT.

02487

OX40 Checkpoint Molecule Targeted Antibodies for Cancer Immunotherapy in Dogs

Principal Investigator: Steven W. Dow, DVM, PhD; Colorado State University

Total Grant Amount: \$168,905

Grant Period: 3/1/2018- 2/29/2020

Project Abstract: Checkpoint molecules play a key role in regulating T cell immunity against cancer (T cells are one type of immune cell called lymphocytes). Clinical trials of antibody therapeutics that target checkpoint molecules such as PD-1 in human oncology (eg, Opdiva, Keytruda) have demonstrated remarkable results in inducing tumor regressions and cures, against a variety of different cancer types. This new era of cancer immunotherapy also has tremendous potential for treatment of cancer in dogs. The investigators will begin development of a new, second-generation immunotherapy targeting the canine checkpoint molecule OX40 (CD134). Development of the first generation PD-1 antibodies for canine oncology is already underway, and the PI's laboratory has been involved in evaluating immune responses to these antibodies. Studies in rodent models indicate that targeting the OX40 checkpoint molecule may be more effective than PD-1 for cancer immunotherapy. The investigators will use antibodies generated in their lab against the canine OX40 checkpoint molecule to investigate its role in regulating cancer immunity in dogs, as a first step in advancing OX40 antibodies to clinical trials in dogs with cancer. In this project, they will characterize canine OX40 antibodies, determine which immune cells express OX40 in dogs, determine how OX40 antibodies activate effector T cells in dogs, and how these antibodies trigger immune activation in tumor tissues to help accelerate development of OX40 checkpoint molecule targeted antibodies as next generation cancer immunotherapeutics for dogs.

02456-A

The Impact of Intravenous Anesthetic Agents on Canine Natural Killer Cell Cytotoxic Function: The Achilles Heel in Cancer Diagnosis and Surgery?

Principal Investigator: Oliver A. Garden, BVetMed, PhD; University of Pennsylvania

Total Grant Amount: \$14,945

Grant Period: 1/1/2018- 12/31/2018

Project Abstract: Dogs are often placed under general anesthesia for diagnostic and surgical procedures. Aside from the well-known risks of anesthesia, such as heart or lung depression, anesthetic agents can also suppress immune function. This poorly understood phenomenon is especially important in dogs that may already suffer from immune compromise, such as those with critical illness or cancer. The role of commonly used anesthetic agents, such as ketamine and propofol, on immune function in patients with cancer is being investigated in laboratory animals and humans, with ketamine increasing the spread of cancer to the lungs in rats compared to propofol. Unfortunately, there is no current research in dogs comparing these two anesthetic agents. Additionally, a newer anesthetic agent, alfaxalone, is gaining popularity for use in both healthy and critically ill dogs, but there is no research available on the effects of alfaxalone on immune function in dogs. Given the lack of information of the immune effects of these three anesthetic agents, the objective of this study is to compare the effects of ketamine, propofol and alfaxalone on a type of immune cell that is important in preventing cancer spread (metastasis). Based on the outcome of this research project and further studies, the investigators plan to develop immune-sparing anesthetic protocols to improve outcomes of dogs with cancer undergoing anesthesia for diagnostic procedures or surgery.

02455-A

Identification of Genetic Mutations in Anal Sac Carcinoma in English Cocker Spaniels

Principal Investigator: Shaying Zhao, PhD; University of Georgia

Total Grant Amount: \$15,000

Grant Period: 12/1/2017- 11/30/2018

Project Abstract: English Cocker Spaniels (ECSs) are about 7 times more likely than other dog breeds to develop anal sac carcinoma (ASC). Hence, there appears to be a genetic basis for this disease development in ECSs. The investigators will sequence the genomes and transcriptomes of blood and ASC tumor samples collected from ECS dogs across the US. The samples will be studied alongside the pedigree information and medical records. Using dog-human comparative genomics and oncology strategy for cancer-causative mutation discovery, successful identification of mutations in ASC development in ECSs may lead to the development of genetic tests of this aggressive disease in ECSs and yield targets for therapeutic intervention.

02446

Development of Genetic Biomarkers to Improve Diagnosis and Treatment of Canine Histiocytic Sarcoma

Principal Investigator: Benoit Hédan, DVM, PhD; CNRS - University of Rennes

Total Grant Amount: \$138,107

Grant Period: 5/1/2018- 4/30/2020

Project Abstract: Several breeds of dog, including Retrievers, Bernese Mountain Dogs and Rottweilers, are known to present elevated risks of cancers including histiocytic sarcoma (HS), lymphoma, and hemangiosarcoma. HS may be misdiagnosed due to clinical presentation shared with these other cancers. Due to the aggressiveness of HS and its late diagnosis, there is no known effective treatment. With different prognostic and therapeutic options, an early and accurate diagnosis of cancer is important to select appropriate therapies to improve outcomes for affected dogs, while still being cost effective. There is a need for the development of biomarkers for early and precise detection of such cancers. The research team has identified tumoral DNA alterations specific to HS and will use these unique alterations to improve early diagnosis of HS and to develop more specific therapies. Moreover, the investigators have been able to detect these biomarkers, already used in their lab to discriminate HS, in the blood of affected dogs. The objectives of this study are to develop a non-invasive diagnostic blood test using genetic biomarkers to accurately diagnose HS, and to explore earlier diagnosis to improve treatment outcomes through the selection of targeted therapies.

New

02405-A

Transcriptome Based Diagnostics in Canine Soft Tissue Sarcoma

Principal Investigator: Andrew D. Miller, DVM; Cornell University

Total Grant Amount: \$14,880

Grant Period: 11/1/2017- 10/31/2018

Project Abstract: Sarcomas are malignant cancers that can arise in any part of the body; however, in the dog, a subset referred to as soft tissue sarcomas account for 10-15% of all skin and subcutaneous cancers. Traditionally biopsy and subsequent histology have been the primary means of diagnosing these cancers. The histology is assigned to one of three grades ranging from low (grade I), intermediate (grade II), and high (grade III). Currently, histologic grade is the key criterion for guiding treatment and determining patient outcome. However, in human medicine and pathology, soft tissue sarcomas are diagnosed with a hybrid approach that involves both histologic features and genetic analysis of the tumor sample. This genetic analysis guides further treatment, aids in developing accurate follow-up information, and has been shown to have a positive effect on patient outcome and survival. Unfortunately, despite how common soft tissue sarcomas are in the dog, treatment still relies solely on the histologic grade, which is subjective at best, and genetic data is not incorporated into the diagnostic plan. The objective of this study is to develop a validated test to analyze the genes present in canine soft tissue sarcoma. This will allow for future prospective studies in which genetic analysis will be used to guide treatment in dogs afflicted with this cancer, lead to more refined care, and ultimately improve patient outcome.

02321

Clinical Trial of Procaspace-3 Activator (PAC-1) in Combination with Hydroxyurea for Treatment of Canine Meningioma

Principal Investigator: Timothy M. Fan, DVM, PhD; University of Illinois

Total Grant Amount: \$51,191

Grant Period: 2/1/2017- 1/31/2019

Project Abstract: Primary brain tumors are a significant cause of illness and death in pet dogs, with meningioma accounting for approximately half of the cases seen by veterinary neurologists and oncologists. Although surgery remains the best treatment for dogs with meningioma, some dogs are not good candidates for this approach based on their tumor size and/or location. Dogs also may experience tumor regrowth after an attempt is made to surgically remove the tumor. In these situations, effective treatment options are limited. Thus, new treatments that are both safe and effective are needed for dogs with meningioma. A team of investigators from the National Cancer Institute's Comparative Oncology Program (NCI-COP) and selected veterinary academic centers will work together using state-of-the art imaging and a novel therapeutic approach for dogs with meningioma that are good surgical candidates. Dogs enrolled in this study will receive an investigational combination of chemotherapy agents (PAC-1 + hydroxyurea) and will be monitored with magnetic resonance and non-invasive molecular imaging techniques. Dogs will then undergo tumor removal and tissue analysis. This approach is the first to validate and advance a new therapy that is directly applicable to dogs, and potentially also to humans, with advanced, locally-recurrent, and/or non-resectable meningioma.

02204

Using Enhanced Imaging to Evaluate Tumor Margins for Canine Mammary Cancer and Soft Tissue Sarcoma

Principal Investigator: Laura E. Selmic, BVetMed; Ohio State University

Total Grant Amount: \$46,358

Grant Period: 1/1/2016- 12/30/2018

Project Abstract: Surgery is the primary treatment for many common tumors affecting dogs including mammary tumors and soft tissue sarcomas (STS). For these tumors, the best chance of cure is offered if the surgeon can fully remove both visible and microscopic traces of the tumor. Unfortunately, to do this, surgeons must rely on indirect and crude methods to assess the extent of the tumor during surgery. The success of the procedure will not be known until several days later, following sample assessment by the pathologist. After surgery, decisions regarding the necessity of further treatment and the patient's prognosis are often determined from the pathology results. For malignant tumors, if the disease is minimally or incompletely removed, further surgery or radiation therapy is often required. Additional treatments such as these can result in further risk and discomfort for the patient as well as present emotional and financial costs for owners. Optical coherence tomography (OCT) is an emerging diagnostic imaging tool that uses light waves to generate real-time, high-resolution images of tissue at a microscopic level. These images can be used to evaluate for residual disease at the time of surgery giving immediate feedback to the surgeon. This study will focus on validating this technology for the imaging of surgical margins of two important canine cancers—mammary tumors and STS. If successful, this technology can be used to assess for residual cancer during surgery to benefit patients by guiding accurate treatment recommendations and attempting to reduce the need for additional treatments or surgery, and thus advancing the standard of care for canine patients.

Oncology - Hemangiosarcoma

02519

Prevalence of *Bartonella* spp. Infection in Dogs with Cardiac and Splenic Hemangiosarcomas Within and Between Geographic Locations

Principal Investigator: Edward B. Breitschwerdt, DVM; Matthew Breen, PhD; North Carolina State University

Total Grant Amount: \$219,026

Grant Period: 2/1/2018- 1/31/2020

Project Abstract: Splenic masses comprise ~50% of all canine splenic disease. Despite advances in imaging and pathologic definition, the etiology and medical relevance of splenic lesions in dogs are often ambiguous. While some splenic tumors are benign, approximately two-thirds are highly malignant and carry a poor prognosis. Hemangiosarcoma (HSA) accounts for the majority of canine malignant splenic tumors and occurs in many large dog breeds, including mixed breeds. A less common site of HSA localization is the heart (cardiac HSA). Risk factors for both cardiac and splenic HSA remain unclear, confounding development of preventative strategies. The investigators recently reported a high prevalence of species of the bacterial genus *Bartonella* in dogs with HSA from North Carolina, suggesting a potential role in the initiation and/or progression of this cancer. *Bartonella* species exist worldwide and are transmitted by blood-sucking arthropods (e.g. ticks, fleas) and their presence in splenic tissue could potentially be explained by the fact that the spleen is primarily responsible for removal of blood-borne parasites from the systemic circulation. The investigators will perform a comprehensive examination of the potential association between *Bartonella* infection and HSA by comparing the prevalence of *Bartonella* DNA in tumor and blood samples from both splenic and cardiac HSA cases, and also within and between distant geographical locations in the US. Ultimately, demonstration of a robust association between *Bartonella* infection and the development of HSA may lead to new opportunities for improved diagnosis, treatment and prevention of this devastating cancer.

02510

Identification of Novel Synthetic Lethal Partners to Optimize PI3K Targeted Therapies in Canine Hemangiosarcoma

Principal Investigator: Cheryl A. London, DVM, PhD; Tufts Medical School

Total Grant Amount: \$168,857

Grant Period: 3/1/2018- 2/28/2021

Project Abstract: Hemangiosarcoma (HSA) is a cancer of the cells lining the blood vessels that is very aggressive and has nearly always spread by the time it is diagnosed. HSA accounts for 5-7% of all cancers in dogs resulting in approximately 25,000-50,000 new cases per year. The treatment of choice is surgical removal followed by chemotherapy administration. Unfortunately, despite aggressive therapy, the majority of dogs diagnosed succumb to their disease within 6-8 months. Virtually no improvements in outcome for affected dogs have occurred in the past 30 years despite multiple clinical trials and research efforts. More recently a new therapy has been developed targeting two receptors on HSA cells. However, the majority of dogs still died by 10-12 months after treatment. The molecular pathway known as the PI3K/AKT/mTOR pathway has previously been implicated in the pathogenesis of many forms of cancer including HSA. Indeed, inhibitors of PI3K/AKT/mTOR pathway have some activity against HSA cell lines in the laboratory. The investigators have generated data showing that a subset of canine HSA tumors possess genetic mutations in PI3K that are known to activate the pathway in cancer cells. In this study, they will fully characterize the expression and function of PI3K in canine HSA tumor cell lines and tumor samples. This information will then be leveraged to identify new ways to block the PI3K/AKT/mTOR pathway using a combination of small molecule inhibitors that are most effective at killing tumor cells. These data will then be used to design future clinical trials in dogs with HSA.

02234-MOU

A Novel Approach for Prevention of Canine Hemangiosarcoma

Principal Investigator: Jaime F. Modiano, VMD, PhD; University of Minnesota

Total Grant Amount: \$432,000

Grant Period: 3/1/2016– 8/31/2019

Project Abstract: Hemangiosarcoma, an aggressive form of cancer in dogs, is the cause of death for one out of every five Golden Retrievers in the United States. Portuguese Water Dogs and Boxers also have an especially high risk for this disease which is devastating for all dogs. Hemangiosarcoma is incurable partly because the cancer is detected at a very advanced stage when it is resistant to conventional therapies. Thus, an unconventional approach to improve outcomes for hemangiosarcoma patients will involve effective methods for early detection and for disease prevention. This project will pair two novel technologies consisting of a patented test to detect hemangiosarcoma cells in blood samples, and a treatment that attacks the cells that establish and maintain the disease. Three milestones will be met: first, will be to expand understanding of the performance and utility of the blood test for cancer in dogs with active disease; second will be to confirm the utility of the test to predict disease progression in treated dogs. And third will be to establish the performance of the test in the "early detection" setting (dogs at high risk without evidence of active cancer), and thus measure hemangiosarcoma prevention through eradication of the tumor initiating cells with the targeted, investigational drug. This project will create tools to guide further development, licensing and deployment of these paired technologies against cancer, specifically hemangiosarcoma, with an ultimate goal for disease prevention in all dogs.

Funding for the research is provided through the collaborative efforts and generosity of the American Boxer Charitable Foundation, Golden Retriever Foundation, and Portuguese Water Dog Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.

Oncology - Lymphoma

02502

Precision Medicine for Canine Lymphoma

Principal Investigator: Nicola J. Mason, BVetMed, PhD; University of Pennsylvania

Total Grant Amount: \$86,400

Grant Period: 3/1/2018- 2/29/2020

Project Abstract: The clinical response of dogs with lymphoma to multi-agent chemotherapy is highly variable. Although up to 85% of dogs respond initially, some relapse within weeks, while others enjoy remission times of two years. This heterogeneity in clinical response is in part explained by the recognition that "lymphoma" is not a single disease entity, but consists of different subtypes that can be characterized on a molecular level by mutations in specific genes. As in human medicine, it follows that different lymphoma subtypes, driven by different molecular mechanisms, may respond better to therapies that are specifically selected to inhibit the driver mechanisms within that patient's tumor. Recent work using sophisticated genetic sequencing tools (next-generation sequencing (NGS)) has begun to shed light on the different molecular subtypes of canine B cell lymphoma, and specific therapies aimed at targeting patient-specific driver genes and pathways are being developed. To enable targeted therapies to move into the clinic, a personalized diagnostic tool must be developed that can rapidly and cost-effectively determine the mutational profile of a patient's cancer allowing selection of the most effective drug for that patient. The investigators aim to develop a NGS diagnostic test that can be employed on standard biopsy samples to identify molecular drivers of a patient's lymphoma (personalized diagnostics), enabling the most appropriate targeted therapy to be selected for that patient. In addition, they aim to determine whether specific mutational profiles within canine lymphoma identified by their NGS panel are predictive of clinical outcome.

02318

Genetic and Environmental Risk for Lymphoma in Boxer Dogs

Principal Investigator: Lauren A. Trepanier, DVM, PhD; University of Wisconsin, Madison

Total Grant Amount: \$112,861

Grant Period: 1/1/2017- 12/31/2018

Project Abstract: Lymphoma is a fatal cancer of the blood cells that can occur in any dog. Lymphoma is more common in Boxers, Golden Retrievers, and several other purebreds, which suggests involvement of inherited genes. Recent research has focused on gene mutations in the tumors of dogs with lymphoma. However, we do not understand why these mutations accumulate in certain dogs, and this understanding is essential for disease prevention. Canine lymphoma resembles Non-Hodgkin lymphoma (NHL) in humans, which is more common in industrialized countries and is associated with chemicals found in tobacco smoke, certain household products, pesticides, herbicides, and fungicides. Glutathione-S-transferases (GSTs) are enzymes that can break down toxic chemicals in the body and prevent tumor mutations. Inherited gene defects in the 3 major GST enzymes, GST-theta, GST-pi and GST-mu, each increase NHL risk, and simultaneous defects in more than one enzyme further increase NHL risk. The investigators have characterized two GST-theta enzymes in dogs, and both have defective gene variants. So far, their findings suggest one variant is a risk factor for lymphoma in dogs of varying breeds. However, the genes for canine GST-pi and GST-mu enzymes have not yet been explored. This research will determine whether defective GST genes along with certain household and yard chemicals are associated with lymphoma in dogs, with a focus on the high-risk Boxer breed. The overall goal of this study is to identify combinations of genes and environmental chemicals that contribute to the development of lymphoma in dogs, so that better cancer prevention strategies can be developed.

02317

The Role of Complex Translocations Associated with TP53 Somatic Mutations for Aiding Prognosis of Canine Diffuse Large B-Cell Lymphoma

Principal Investigator: Matthew Breen, PhD; North Carolina State University

Total Grant Amount: \$177,327

Grant Period: 1/1/2017- 12/31/2018

Project Abstract: Lymphoma accounts for up to 24% of all cancers diagnosed in pet dogs. Among these cases diffuse large B-cell lymphoma (DLBCL) is the most common subtype. Despite continued advances in veterinary medicine, the response to treatment for canine lymphoma remains highly variable with no reliable means to predict response. Studies of lymphoma in people have identified characteristic genome changes that have both diagnostic and prognostic significance. In human DLBCL, mutations in the TP53 gene, and genome rearrangements involving the MYC, BCL2 and BCL6 genes have been shown to confer particularly poor prognosis in cases treated with standard of care multi-agent (CHOP-based) chemotherapy. The investigator's previous CHF-funded studies have shown that canine cancers, including lymphoma, exhibit genomic changes that are conserved with those observed in the corresponding human cancers, and have identified MYC and BCL2 rearrangements and a high frequency of TP53 mutation in canine DLBCL. This research will screen a well-defined collection of over 450 pre-treatment, canine DLBCL samples to determine accurate frequencies of these genome changes. The researchers will investigate the correlation of these target aberrations with duration of first remission, and identify key genomic signatures that may aid prognosis of prospective canine lymphoma cases. The data generated should assist owners and veterinarians with decisions regarding treatment with CHOP. Patients with signatures predictive of poor response to conventional CHOP chemotherapy may benefit from more aggressive treatment at the outset to improve outcome.

02316

Genetic Risk Factors for Canine T zone Lymphoma

Principal Investigator: Anne A. Avery, DVM, PhD; Colorado State University

Total Grant Amount: \$52,894

Grant Period: 1/1/2017- 12/31/2018

Project Abstract: The Golden Retriever is a breed that develops a variety of cancers at a high frequency. One type of cancer, T zone lymphoma, is so common in this breed that 40% of all cases are seen in Golden Retrievers. This observation suggests a clear genetic predisposition. The investigators have completed an environmental risk factor study and the first phase of a genetic risk factor study to better understand the causes of this disease. Two key findings from this work are, 1) The same genetic region associated with risk for mast cell tumors was identified as conferring risk for T zone lymphoma, and 2) The presence of hypothyroidism was protective for T zone lymphoma, and genes associated with thyroid function are also found in the risk regions. The goal of this study is to complete the genetic risk factor study by identifying specific genetic mutations associated with the disease. This research will improve understanding of the mechanisms that lead to T zone lymphoma as well as mast cell tumors in dogs.

02309

Targeting the Cancer Epigenome: The Effect of Specific Histone Lysine Methyltransferase Inhibition in Canine B-Cell Lymphoma

Principal Investigator: Angela McCleary-Wheeler, DVM, PhD; Cornell University

Total Grant Amount: \$78,069

Grant Period: 1/1/2017- 12/31/2019

Project Abstract: Canine lymphoma is one of the most common cancers in dogs. While some breeds appear more at risk than others, all can be affected. Although it is often treatable, canine lymphoma can rarely be cured. A continued understanding of the mechanisms causing lymphoma in dogs and identification of novel therapies are needed to improve survival in dogs with lymphoma. One area of research that has been actively explored and provided exciting breakthroughs for human lymphoma is epigenetics, or alterations in how genes are turned on and off independent of the DNA sequence. One way in which this occurs is due to modifications of the proteins that interact with DNA called histones. Various modifications to these histones can result in genes being turned on or off, leading to the development of cancer. One particular enzyme that modifies histones, EZH2, has been found to play a role in some human lymphomas. However, this has been unexplored in canine lymphoma. Given the striking similarities between human and canine lymphoma, the objective of this work is to characterize the function and role of EZH2 in canine lymphoma. The investigators will utilize an EZH2 inhibitor to study EZH2 in canine lymphoma cells. The information obtained from this study will help guide the future development of this targeted inhibitor for use as a novel therapy to treat canine lymphoma.

01418

Harnessing a Dog's Own Immune System to Kill Lymphoma Tumor Cells

Principal Investigator: Heather M. Wilson-Robles, DVM; Texas A&M Research Foundation

Total Grant Amount: \$150,000

Grant Period: 1/1/2011– 12/31/2018

Project Abstract: Lymphoma is the most common malignancy of dogs representing up to 25% of diagnosed cancers. Dogs often develop an aggressive form of lymphoma that is rarely curable, with most unfortunately succumbing to disease within 12 months of diagnosis despite best-available chemotherapies. Dr. Wilson-Robles will develop a new treatment to re-train the dog's own immune system to attack the most common type of canine lymphoma, B-cell lymphoma. In order to accomplish this they will obtain a small number of circulating white blood cells, called T-cells, from the blood of affected dogs and insert a gene that will cause the T-cell to express a receptor which recognizes the tumor "fingerprint". After docking with the lymphoma, the T-cell will be triggered to mount an immune response against the tumor cells with the specific fingerprint. This therapy could be used alone or in combination with chemotherapy. Preliminary data demonstrates that it is possible to genetically modify T-cells. Further, they have been able to successfully harvest and grow T-cells in the laboratory and return them safely to the dog. These infused cells can be found in the blood and tumor weeks after infusion, showing that it is possible for these cells to survive in the dog. If successful this study will be the first to develop an "in-dog" T-cell therapy targeting a tumor that has historically thought to be untreatable.

Oncology - Osteosarcoma

01660

Identifying the Genes That Confer Risk for Osteosarcoma

Principal Investigator: Carlos E. Alvarez, PhD; The Research Institute at Nationwide Children's Hospital

Total Grant Amount: \$120,000

Grant Period: 1/1/2012- 12/31/2019

Project Abstract: Osteosarcoma (OSA) is the most common cancer of the bone in both dogs and humans. A prime candidate for investigation of the genetic component of OSA is the Greyhound, which has the highest risk of OSA of any breed. However, despite significant effort, classical genetic approaches have not identified any Greyhound variant that accounts for most OSA cases in that breed. Dr. Alvarez proposes that Greyhound OSA variants have been directly or indirectly selected for in racing performance, consistent with the vastly elevated incidence in racing vs. show Greyhounds. If this is true and all racers carried an OSA mutation on both chromosomes, then this could not be detected using classical approaches (which require different genetic markers to distinguish cases v. controls). Here Dr. Alvarez proposes an innovative genetic approach that is impervious to the limitations described above, and enables genome-wide discovery of Greyhound variation with large effects on OSA risk. Such findings would lead to rapid development of therapies and clinical trials in dogs, and translation to human medicine.

02517

Genetics of Primary Angle Closure Glaucoma in the Siberian Husky

Principal Investigator: Gillian McLellan, BVMS, PhD; University of Wisconsin, Madison

Total Grant Amount: \$121,740

Grant Period: 3/1/2018—2/29/2020

Project Abstract: Glaucoma is a very painful and rapidly blinding disease that leads to irreversible sight loss in many thousands of dogs in the USA and worldwide each year. Current medical and surgical treatments that target the damaging high pressure in the eyes of affected dogs are not able to cure the disease but only control it. In many dogs with glaucoma, surgical removal of both eyes is needed to control pain. Past research reveals that the Siberian Husky is one of the more commonly affected breeds in both North America and Europe. With improvements in canine DNA sequencing tools, it is now possible to carry out very detailed sequencing of DNA of individual dogs, and these techniques have identified mutated genes responsible for several dog diseases. The investigators in this study will analyze DNA from Siberian Huskies with glaucoma and compare it to DNA from dogs without glaucoma. The goal is to identify the DNA mutation (or mutations) that cause glaucoma and, in turn, develop a genetic test for the disease in this breed and possibly other affected breeds such as the Samoyed and Shiba Inu. A DNA test would provide an important tool in efforts to fight this disease as dog breeders could develop more informed breeding strategies, with a goal to ultimately help eliminate this disease from the dog population.

02432-A

New

Tears as a Source of Biomarkers for Dry Eye in the Dog

Principal Investigator: Francesca Capaldo, DVM; Animal Health Trust

Total Grant Amount: \$13,837

Grant Period: 6/1/2018- 5/31/2019

Project Abstract: Dry eye (DE) or keratoconjunctivitis sicca (KCS) is a painful disease in dogs and humans where insufficient tear production can cause pain, corneal ulceration and blindness. KCS in dogs is commonly immune-mediated, where the dog's immune system attacks the tear glands. However, the mechanism by which this occurs is not well understood. In humans, long term use of ocular medications containing the preservative Benzalkonium Chloride (BAC) may trigger DE. While no studies have been conducted to explore whether a correlation between BAC and DE exists in dogs, long term ocular treatment for dogs with BAC-containing drugs may cause ocular surface inflammation resembling KCS. The treatments available for KCS (immunomodulating and tear replacement drugs, and surgery) are often not completely effective. The investigators will look for and measure proteins in the tears of dogs affected by presumptive immune-mediated KCS, and the tears of dogs on long term ocular medications containing BAC. This work will help improve understanding of the pathogenesis of KCS and allow development of a non-invasive diagnostic test, which can also be used to monitor progression of the disease and response to treatment.

02403-MOU

Microphthalmia and Delayed Growth Syndrome in the Portuguese Water Dog

Principal Investigator: Margret L. Casal, DVM, PhD; University of Pennsylvania

Total Grant Amount: \$12,960

Grant Period: 11/1/2017- 10/31/2019

Project Abstract: Microphthalmia and delayed growth syndrome (aka "puppy eye syndrome") has been reported by Portuguese Water Dog breeders dating as far back as 1986. However, there is no information in the scientific literature and the majority of data concerning this syndrome has been obtained from records of breeders, which have anecdotal reports of the disease and little, if any, medical diagnostics. Affected dogs present with microphthalmia of varying severity, other eye abnormalities, short stature and other findings. To date, the investigators have been able to collect DNA from 24 affected dogs. Males and females can be affected, although females predominate (about 70%). Preliminary pedigree studies suggest an autosomal recessive inheritance. Human literature reports numerous syndromes associated with microphthalmia, and many genes have been identified as having a causative role. The goals of this investigation are to better characterize the clinical syndrome seen in Portuguese Water Dogs, confirm a suspected mode of inheritance, obtain additional samples for investigation into the genetic mutation, and develop a mutation based, genetic test for breeders to eliminate this syndrome from the Portuguese Water Dog breed.

Funding for the research is provided through the collaborative efforts and generosity of the Portuguese Water Dog Foundation, Inc., and the Portuguese Water Dog Club of America. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.

02340

Clinical and Genetic Background of Progressive Retinal Atrophy in Miniature Schnauzers

Principal Investigator: Hannes T. Lohi, PhD; Folkhälsan Institute of Genetics

Total Grant Amount: \$46,224

Grant Period: 12/1/2017- 11/30/2018

Project Abstract: Dogs may be affected with hereditary eye disorders, which cause severe vision impairment, and sometimes progress to complete blindness. One hereditary condition is progressive retinal atrophy (PRA), in which the light-sensing receptors in the retina are lost, leading to complete blindness. Currently there are no treatment options for this disease. The development of genetic testing would be an important breakthrough for veterinary medicine. The identification of a causative gene would also enable a study of the molecular background of the disease for improved treatment plans. The investigators have established a large pedigree and clinically-investigated sample cohort in Miniature Schnauzers with PRA to identify its genetic cause, and have already identified the chromosomal region suspected to harbor the causative gene. Through this study, the researchers hope to identify a PRA gene and mutation, leading to a genetic test for the eradication of this disorder from the Miniature Schnauzer breed.

02336

Genetics of Primary Angle Closure Glaucoma in American Cocker Spaniels

Principal Investigator: Sara M. Thomasy, DVM, PhD; University of California, Davis

Total Grant Amount: \$40,000

Grant Period: 5/1/2017- 4/30/2019

Project Abstract: Glaucoma is a leading cause of irreversible blindness and globe removal (enucleation) in dogs. Primary angle closure glaucoma (PACG) is the most common form of glaucoma in dogs whereby acute blockage of the iridocorneal angle leads to a rapid increase in intraocular pressure. Consequently, PACG is painful, demands immediate medical attention, and often causes incurable vision loss. The American Cocker Spaniel (ACS) has the highest reported prevalence of any canine breed for PACG. The investigators will study the genetics of PACG in the ACS to identify potential disease-causing loci and variants. Dogs will be extensively phenotyped as PACG cases or controls using advanced imaging equipment used to investigate glaucoma in human patients. Identification of genetic markers associated with PACG in ACSs will facilitate the development of a genetic test to inform breeding programs. Furthermore, identification of the molecular basis of PACG may help elucidate novel therapeutic or testing strategies in the management of this blinding disease that may be translatable to the human condition.

02164-MOU

Determining the Genetic Contribution to Boxer Corneal Ulcers

Principal Investigator: Kathryn M. Meurs, DVM, PhD; North Carolina State University

Total Grant Amount: \$68,053

Grant Period: 1/1/2015– 12/31/2018

Project Abstract: Spontaneous chronic corneal epithelial defects (SCCEDs) are chronic corneal ulcers that fail to undergo normal healing that are commonly observed in Boxers. The predilection for Boxers suggests that SCCEDs is inherited in this breed. Affected dogs develop spontaneous corneal ulcers that are often exceptionally painful and persist for weeks to months. Most dogs require surgical therapy to heal the corneal ulcer and experience corneal scarring as a result. The impact on the quality of life for dogs during episodes of ulceration has led to increased interest in disease prevention. However, since SCCED is an adult onset disease, many dogs are selected for breeding before they are diagnosed. A blood test that could identify affected animals before they are used for breeding would greatly decrease the prevalence of SCCEDs. In a previous study funded by the AKC-CHF Dr. Meurs and colleagues collected samples from adult boxers with and without SCCED and performed a genome wide association study. In the study proposed here they will perform whole genome sequencing (GWAS) on a subset of affected and unaffected dogs and use the data from the GWAS to focus in on important variants. They will then more closely evaluate variants of interest to determine the gene and ultimately the causative genetic mutation. They hope that the identification of a genetic cause for SCCEDs in the Boxer can be used to reduce the prevalence of this disease in this breed but also to provide information for other affected breeds.

Funding for the research is provided through the efforts and generosity of the American Boxer Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.

02512-A

Genome Sequencing and Antimicrobial Susceptibilities of *Escherichia coli* Isolated from Clinical Cases of Canine Pyometra

Principal Investigator: Erin E. Runcan, DVM; Ohio State University

Total Grant Amount: \$8,208

Grant Period: 12/1/2017- 11/30/2018

Project Abstract: Pyometra is a potentially life-threatening infection of the canine uterus by bacteria, most commonly *Escherichia coli* (*E. coli*). In humans with recurrent infections, *E. coli* produces biofilm, a layer of polysaccharide that protects the organism from the host immune system as well as antibiotic agents, decreasing treatment efficacy. Current treatments for pyometra are costly, time-consuming, and not without risk to the bitch. The investigators postulate that biofilm production by *E. coli* within the uterine lining may be responsible for perpetuating the disease and making treatment difficult. In a previous CHF-funded study, the investigators were able to prove that *E. coli* from clinical cases of canine pyometra is capable of producing biofilm both in the uterus and in laboratory settings. The investigators will characterize the presence of ten different genes associated with biofilm production and disease-contributing factors of *E. coli* organisms to determine if there is an association with those strains of *E. coli* that produce biofilm, and certain disease factors found in other strains of *E. coli*. Disease factor genes and resistance patterns identified may serve as targets for new therapeutics directed at the disruption of biofilm in an effort to shorten the duration of treatment of pyometra.

02409-A

Targeting Bacterial Adhesion via Blocking the Scavenger Receptor Type B1 in Canine Pyometra

Principal Investigator: Cordula Gabriel, PhD; University of Veterinary Medicine, Vienna

Total Grant Amount: \$14,904

Grant Period: 1/1/2018- 2/29/2020

Project Abstract: Pyometra is the most common uterine disease in intact bitches leading to potentially life-threatening complications via the systemic inflammatory response syndrome (SIRS). *Escherichia coli* (*E. coli*) is the most abundant isolated pathogen causing pyometra. In a previous study the investigators characterized endometrial epithelial foam cells (EEFCs) in the canine endometrial surface occurring in metestrus, the cyclic stage with the most common presence of pyometra. They identified a specialized receptor named scavenger receptor class B1 (SR-B1) expressed in EEFCs. SR-B1 is relevant for lipid-uptake and thereby involved in EEFC formation. SR-B1 is also a strong binding partner for *E. coli*, and a significant upregulation of SR-B1 in pyometra affected canine uteri was identified. The hypothesis in this study is that blocking of SR-B1 in EEFCs can be used as supportive non-invasive pyometra treatment. Binding capacity of an adherent pyometra-related *E. coli* strain will be tested in the presence of the functional SR-B1 and in cells in which the SR-B1 is blocked in vitro. The mechanisms behind SR-B1 upregulation will be investigated to gain more information about this pyometra-related target molecule. Multidisciplinary analyses will be applied to identify the effects of blocking SR-B1 on *E. coli* adherence and inflammatory cytokine release. The reduction of the inflammatory response via blocking the endometrial SR-B1 could be a further benefit of this novel therapeutic approach.

02193-A

Identifying the Genetic Basis of Fetal Anasarca in Bulldogs/Canines

Principal Investigator: Anna V. Kukekova, PhD; University of Illinois

Total Grant Amount: \$12,960

Grant Period: 10/1/2015- 9/30/2018

Project Abstract: Dystocia is one of the most significant reproductive health concerns for dog owners and breeders. While there can be many causes of dystocia, the occurrence of so-called "water" or "walrus" puppies is one of the more common reasons within particular breeds. Water puppies suffer from the abnormal accumulation of body fluids, called anasarca, resulting in a generalized swelling of the body. Normal delivery through the birth canal then becomes difficult or even impossible, oftentimes requiring intervention by caesarean section. Water puppies are generally stillborn or die shortly after birth. While anasarca affects many dog breeds, it appears to be more frequent in brachycephalic breeds including the Bulldog, French bulldog, Pug, Boston terrier and others. Due to the known genetic relationship between these breeds and the recurrence of anasarca puppies in specific matings, it is strongly believed that there is a significant genetic risk factor associated with this problem. Modern genetic tools and techniques have greatly improved the ability to identify specific variations in DNA which may be responsible for such traits. Thus, in an effort initiated by the Bulldog Club of America and Bulldog Club of America Charitable Health Fund, samples from newborn puppies with anasarca, their parents, and non-affected puppies have been collected, and will be utilized to analyze for a genetic basis of anasarca in an effort to develop a DNA-based test that can be used to screen for and reduce the incidence of this devastating disease.

Tick-Borne Disease Initiative

02528

New

Developing a Next Generation Sequencing Diagnostic Platform for Tick-Borne Diseases

Principal Investigator: Pedro Paul Diniz, DVM, PhD; Western University of Health Sciences

Total Grant Amount: \$120,983

Grant Period: 6/1/2018– 5/31/2020

Project Abstract: Diagnostic tests based on the detection of DNA from harmful organisms in clinical samples have revolutionized veterinary medicine in the last decades. Currently, diagnostic panels for several vector-borne organisms are available through universities and private labs in the USA and abroad. However, the vast majority of results from sick dogs are negative, which frustrates veterinarians and dog owners trying to reach a definitive diagnosis. These panels are based on the detection of previously known DNA sequences of each pathogen, which limits their ability to detect novel organisms. In this study, the investigators will adapt high-throughput next-generation sequencing (NGS) to the detection of tick-borne bacteria in dog blood in an effort to overcome the limitations of current diagnostics for tick-borne diseases. If successful, increasing the capabilities of NGS to detect infected dogs and to accurately determine which bacteria are responsible for disease will support the development of a better diagnostic tool to simultaneously advance canine and human health. This work expands on Dr. Diniz's previous CHF-funded study #02292.

02386-A

Surveillance of *Hepatozoon americanum* in Populations of the Gulf Coast Tick

Principal Investigator: Andrea Varela-Stokes, DVM, PhD; Mississippi State University

Total Grant Amount: \$12,960

Grant Period: 2/1/2018- 1/31/2020

Project Abstract: American Canine Hepatozoonosis is a debilitating tick-borne disease with poor prognosis and limited treatment options. Affected dogs usually experience fever, muscle pain, and body wasting, and some dogs may have a thickening of their long bones. While most tick-borne diseases occur after transmission of the disease agent during tick feeding, in American Canine Hepatozoonosis, dogs are infected by eating the tick vector carrying the disease agent. *Hepatozoon americanum* causes American Canine Hepatozoonosis. It is a protozoan parasite carried by the tick species, *Amblyomma maculatum*, also known as the Gulf Coast tick. The percentage of Gulf Coast ticks carrying *H. americanum* is unknown. The investigators will use an optimized test to perform active surveillance on Gulf Coast ticks collected in Mississippi during the summer seasons of 2018 and 2019, when adult Gulf Coast tick stages are active. Veterinary summer research students will also participate in the research each year. By involving veterinary students and obtaining active surveillance data on tick populations, the researchers will fill an important gap in the knowledge of American Canine Hepatozoonosis, and increase veterinary and public awareness of potential risk in canine patients.

02383

Identifying Cellular Mechanisms of Inflammation During Canine Tick-Borne Diseases

Principal Investigator: Christine A. Petersen, DVM, PhD; University of Iowa

Total Grant Amount: \$207,526

Grant Period: 9/1/2017- 8/31/2019

Project Abstract: Tick-borne diseases are found in all 50 states of the United States and are the most common vector-borne disease diagnosed in people in the US. The predominant disease is Lyme disease, caused by *Borrelia burgdorferi* and related species (*sensu lato*). Other important canine tick-borne diseases include those caused by *Anaplasma platys*, *Anaplasma phagocytophilum* (*Anaplasmosis*), *Babesia canis*, *Babesia conradae* and *Babesia gibsonii* (*Babesiosis*), and *Ehrlichia canis*, *Ehrlichia chaffensis* and *Ehrlichia ewingii* (*Ehrlichiosis*). Many of these diseases also affect people. Dogs can serve as sentinel species for human disease and there are many areas where the immune responses and disease outcomes are very similar in people and dogs, meaning that important lessons can be learned by sharing information between human and animal health (One Health). The researchers will further investigate the dog's immune system to determine which immune cells are responsible for the cure or creation of canine tick-borne disease. Through understanding which cells are responsible for causing disease, the goal is to then specifically target the molecules they produce using immunotherapy or immune modulation to improve treatment of tick-borne diseases in all dogs.

02284-A

Lyme Disease in Dogs: Prevalence, Clinical Illness, and Prognosis

Principal Investigators: Thomas Wittum, MS, PhD; Andréia Arruda, DVM, MSc, PhD; Ohio State University; Jason Stull, VMD, MPVM, PhD; Ohio State University and University of Prince Edward Island

Total Grant Amount: \$14,148

Grant Period: 7/1/2016- 6/30/2019

Project Abstract: Lyme disease (or Borreliosis) is a bacterial disease of dogs and humans that is transmitted by tick bites. In people, Lyme is the most common tick-transmitted disease in the US, with over 25,000 cases in 2014. While most common in the northeastern coastal states and the upper Midwest, Lyme disease is moving into other regions of the U.S. and Canada. Dogs infected with Lyme disease rarely show signs of illness (typically lameness), but can be severe (e.g., kidney disease). Diagnosis, treatment and prevention of Lyme disease in dogs are complicated by limited research and conflicting professional guidance. Current practices may unnecessarily place dogs at risk for illness and negative outcomes. The investigators will follow a large group of dogs from different regions of the U.S. and Canada. During this period the investigators will determine how often healthy dogs test positive for Lyme disease (meaning they have been bitten by an infected tick) and identify how often they later develop a Lyme-related illness. The risks and benefits of management strategies for Lyme-positive dogs and obstacles to effective tick prevention will be determined to help clarify unmet pet owner education needs. These findings are likely to extend to better understanding of canine and human Lyme disease, and improve health outcomes. Collectively, this work will allow us to identify, define and improve upon best practices for prevention and control of Lyme disease in areas with different Lyme risks, ultimately improving the health of dogs and people.

01780

Defining the Mechanism by Which Ticks Locate Dogs in Order to Better Prevent Disease Transmission

Principal Investigator: Emma Natalie Ivy Weeks, PhD; University of Florida

Total Grant Amount: \$104,867

Grant Period: 3/1/2013- 2/28/2019

Project Abstract: The brown dog tick (BDT) is common across the U.S. and is the most widely distributed tick in the world. BDT's carry and transmit the pathogens that cause debilitating diseases such as canine *ehrlichiosis* and *babesiosis*. Prevention of these diseases is accomplished through tick control. BDT's can complete their entire life cycle indoors, making management difficult. Records of infestations are increasing and unpublished data indicates that a high level of pesticide resistance is present in domestic populations. Consequently once introduced, these ticks are particularly hard to eradicate and as one female tick may lay 5,000 eggs, the problem soon gets out-of-hand. Pesticide resistance leads to aggressive treatment regimes, which in turn, lead to increased exposure of humans and pets to chemical residues. Alternatives to pesticides are needed. Studies have shown that BDT's are attracted to dog odor, a blend of volatile chemicals used by ticks to find a blood meal. In this study, Dr. Weeks will identify the chemicals BDT's use to locate a dog. This will enable manipulation of tick behavior thereby facilitating management and reducing the need for extensive use of pesticides. Improved tick control without the need for increased environmental pesticide applications will improve the quality of life for dogs and their owners.

CHF Clinician-Scientist Fellowship Program

The AKC Canine Health Foundation Clinician-Scientist Fellowship Program supports young scientists. Through this effort our mission to prevent, treat and cure canine disease will endure for years to come.

Recipients are selected based upon the following criteria for a resident/graduate student:

- 1) Enthusiasm for pursuing a career in canine health research,
- 2) Research aligns with CHF's mission to advance the health of all dogs,
- 3) Research abides by CHF policies, including our Humane Use of Animals Policy.

2018 AKC Canine Health Foundation Clinician-Scientist Fellows



Kathryn Dalton, VMD, MPH; Johns Hopkins Bloomberg School of Public Health
Mentor: Meghan Davis, DVM, MPH, PhD

Dr. Kathryn Dalton received her VMD from the University of Pennsylvania. Dr. Dalton's work focuses on how microbial communities are transmitted among animals, humans and the environment, relating microbial community profiles to human and canine health outcomes.



Shelby Gasson, DVM; Texas A&M University
Mentor: W. Brian Saunders, DVM, PhD, Diplomate ACVS

Dr. Shelby Gasson received her DVM from Texas A&M University. She is this year's AKC Canine Health Foundation GCHP Hill Country's Let's Get Ready To Rumble "Rumble" Clinician-Scientist Fellow (akcchf.org/rumble). Dr. Gasson's work focuses on the development of tissue engineering constructs for treatment of osteochondral defects. Dr. Gasson will be evaluating growth and differentiation of canine mesenchymal stem cells on different tissue scaffolds.



**GCHP Hill Country's
Let's Get Ready To Rumble**



Mariah Gentry, DVM; University of Pennsylvania
Mentor: Margret L. Casal, DVM, PhD, Diplomate ECAR

Dr. Mariah Gentry received her DVM from Cornell University. Dr. Gentry's work focuses on the heritability of renal dysplasia in Cairn Terriers and aims to develop a DNA-based marker test so the disorder can be diagnosed at an early age. The findings of this work would allow for more informed breeding decisions as well as make lifestyle changes earlier to prolong the lives of dogs with this disorder.



Sita Withers, BVSc(Hons); University of California, Davis
Mentor: Robert B. Rebhun, DVM, PhD, Diplomate ACVIM (Oncology)

Dr. Sita Withers received her BVSc(Hons) from Melbourne University, Werribee. Dr. Withers' research aims to build a better understanding of how naturally occurring canine cancers can contribute to the study of immunotherapeutics in dogs as well as people. Her research is focused on the immune microenvironment in canine osteosarcoma both in the primary and metastatic sites.

To Support this Program go to: akcchf.org/clinsci

AKC/AKC CHF/TF Theriogenology Residency Program

This program is a collaboration between the American Kennel Club, the AKC Canine Health Foundation, and the Theriogenology Foundation to increase the number of trained practitioners in companion animal theriogenology and clinical genetics. Theriogenology is the branch of veterinary medicine concerned with reproduction, including the physiology and pathology of male and female reproductive systems, and the clinical practice of veterinary obstetrics, gynecology, and andrology.



2018 Theriogenology Residents



Alyssa Helms, DVM; (CHF Grant 02390-E)

Residency Coordinator: Julie T. Cecere, DVM, MS; Virginia-Maryland College of Veterinary Medicine

Total Grant Amount: \$99,036

Grant Period: 7/1/2018- 6/30/2021

Dr. Alyssa Helms attended the University of Tennessee for both her undergraduate degree in animal science (summa cum laude) and her veterinary degree. She has extensive experience in dog training and works with canine breeders to educate on the preservation of purpose-bred dogs and canine reproductive medicine.



Katie Withowski, DVM; (CHF Grant 02395-E)

Residency Coordinator: Scott Bailey, DVM, MS; North Carolina State University

Total Grant Amount: \$100,000

Grant Period: 7/1/2018- 6/30/2021

Dr. Katie Withowski completed her veterinary degree at St. George's University School of Veterinary Medicine after receiving her bachelor of arts from Stony Brook University. During her undergraduate experience, Dr. Withowski also worked as a veterinary assistant. Most recently, she spent a year in field service and completed a theriogenology internship at the University of Georgia.

2016 Theriogenology Residents



Carla Barstow, DVM; (CHF Grant 02282-E)

Residency Coordinator: Robyn R. Wilborn, DVM, MS; Auburn University

Total Grant Amount: \$100,000

Grant Period: 7/1/2016- 6/30/2019

Dr. Carla Barstow has been showing and breeding Samoyeds for over 20 years. Prior to obtaining her DVM degree, she spent 10 years working in the veterinary field as a technician. Dr. Barstow then pursued her DVM degree at the University of Minnesota. Upon graduation, Dr. Barstow returned to Tampa to join a private practice which emphasized reproduction, and enjoyed a heavy theriogenology caseload prior to starting her residency.



Tessa Fiamengo, DVM; (CHF Grant 02294-E)
Residency Coordinator: Marco A. Coutinho da Silva, DVM, PhD; Ohio State University
Total Grant Amount: \$100,000
Grant Period: 7/1/2016- 6/30/2018

Dr. Tessa Fiamengo graduated with honors from Colorado State University with a major in Biology and minors in Biomedical Sciences and Philosophy. She earned her veterinary degree from Oregon State University, and has worked as a small animal general practitioner in Portland, OR.



Victor Stora, DVM; (CHF Grant 02283-E)
Residency Coordinator: Margret L. Casal, DVM, PhD; University of Pennsylvania
Total Grant Amount: \$100,000
Grant Period: 7/1/2016- 6/30/2018

Dr. Victor Stora received his Bachelor of Science from Wagner College, Staten Island, NY, with a double major in Molecular and Cellular Biology and Biochemistry. He received his veterinary degree from the School of Veterinary Medicine, Louisiana State University. He completed a small animal medicine and surgery internship at Virginia-Maryland College of Veterinary Medicine. Dr. Stora breeds Shetland Sheepdogs.



Karen Von Dollen, DVM; (CHF Grant 02281-E)
Residency Coordinator: Scott Bailey, DVM, MS; North Carolina State University
Total Grant Amount: \$100,000
Grant Period: 7/1/2016- 6/30/2019

Dr. Karen Von Dollen attended Bryn Mawr College in Pennsylvania, where she majored in chemistry with minors in mathematics and biology and was a member of the varsity lacrosse team. She returned to California to earn her DVM degree from the University of California, Davis. Following graduation, she completed internships at Alamo Pintado Equine Medical Center in Los Olivos, California and Goulburn Valley Equine Hospital in Victoria, Australia.

To Support this Program go to: akcchf.org/therio

Impact of CHF Funding: Selected 2017-2018 Scientific Publication Outcomes of Research

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